RIGHT INFERIOR FRONTAL GYRUS AND MOTOR RESPONSE INHIBITION

A REAL-TIME FMRI NEUROFEEDBACK STUDY

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[05.05.2014]

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Acknowledgmenets

I would like to thank Associate Professor Tor Endestad (supervisor) for support, advice, feedback, writing critique, and most of all, for making my ambitious project a possibility. The topic, theory, hypothesis, design, development, programming, piloting, testing, analysis and writing of the thesis was done by the author, as well as the implementation of the real-time fMRI capabilities at the Intervention Center, Rikshospitalet Oslo.

I would like to thank Abubakr Eldiriri for help in setting up the XTC framework for online data dumping and Frederic Courivaud for help in adjusting the functional imaging protocol, as well as patching the scanner to circumvent system quirks. I would like to thank Grethe Løvland for letting me play around with the scanner and software, where Murphy's Law was in full effect. I would also like to thank Daniel Corneliussen, Ana Padroa Rocha, Marie Eikemo and Espen Eilertsen for participation in tedious piloting sessions.

I would like to thank Dag Alnæs (co-supervisor) for support, advice and valuable discussions throughout the process, and also in helping with correction of the written text. I would like to thank Ines Blix and Cecilie Skaftnes for looking through my thesis. I value your input greatly! I would finally like to thank Ana Padroa Rocha for endless moral support during long days and nights.

I thank thee all!

Abstract

The ability to stop or override our dominant behavioral responses in face of new unexpected information is a crucial skill in daily life. Impaired response inhibition has generally been associated with several neurological conditions like attention hyperactivity disorder and obsessive compulsive disorder. One particular brain area, the right inferior frontal gyrus (rIFG), has been proposed to support such functionality. However, response inhibition has been argued to be confounded with attentional reorienting. To resolve this debate, the present study investigated whether it is possible to control the hemodynamic response in the rIFG with the use of real time functional magnetic resonance imaging (rt-fMRI) neurofeedback (NF), and if successful up-regulation was associated with a measurable improvement in a response inhibition task and an attention reorienting task. 30 participants completed two days of NF training and were tested before and after on a stop-signal task (SST) and a Posner cueing task (PCT). Results showed that only men in the experimental condition had improved response inhibition efficiency but decreased attentional reorienting efficiency, suggesting gender specific effects of rt-fMRI NF training, and prompting a reevaluation of rIFG's role in attention reorienting and response inhibition. It is proposed that the rIFG is involved in neither response inhibition *nor* attention reorienting, but rather implementing top-down control of behavior, where response inhibition and attentional reorienting is only a few aspects.

Contents

Introduction

Imagine cruising down a highway in which you are changing lanes in order to speed past the elderly man driving in the car in front, when you suddenly notice a car in your side mirror causing you to change your mind mid-action. The ability to slow down or inhibit preprogrammed dominant behavioral motor responses (such as changing lanes) is important when faced with unexpected situations, and a lacking ability to do so might pose a disadvantage in daily life (such as death). Several studies have demonstrated impaired response inhibition in patients with various psychiatric and neurological conditions, among them attentional deficit hyperactivity disorder (ADHD)(Aron & Poldrack, 2005), schizophrenia (e.g. Kaladjian et al., 2007), and obsessive-compulsive disorder (e.g. Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006).

Burle and colleagues (2004) defines motor response inhibition as; "the mechanisms or set of processes that result in the containment of pre-potent behavioral responses when such actions are reflex-like, premature, inappropriate or incorrect". Response inhibition is usually tested with two classic response inhibition tasks; the Go No-go (GNG) task which measures the ability to withhold a dominant response in face of unexpected stimuli, and the stop-signal task (SST) which measures the ability to abort an already occurring or prepared motor response in the face of unexpected stimuli. Inhibition in the GNG task is measured as the rate of omission and commission errors (false and positive errors, respectively) of the go and no-go stimuli, coupled with the speed at which the stimuli is presented and the frequency of the no-go stimuli. The SST on the other hand, utilizes the Horse Race model proposed by Logan and Cowen (1984), which illustrates the stop response as a race between two independent processes; the habitual go-response and the stop-response (figure 1). Whichever of the two processes reaches threshold first "wins the race", hence the name. The stop-response process is assumed to be faster than the go-response process, thus response inhibition efficiency is defined as the amount of time the stop-signal has to occur before the culmination of a response. The Horse Race Model for the SST has been successfully applied in the study of response inhibition in non-human primates (Liu, Heitz, & Bradberry, 2009), children (Carver, Livesey, & Charles, 2009), elderly (Kramer, Humphrey, Larish, & Logan, 1994), and patient groups (Aron & Poldrack, 2005; Chamberlain et al., 2006; Kaladjian et al., 2007). Further, the similarity between response patterns in inhibition of typing, over-learned responses, or incompatible responses, suggests that different types of response inhibition may have common neurological sources (for an overview, see Logan, 1994).

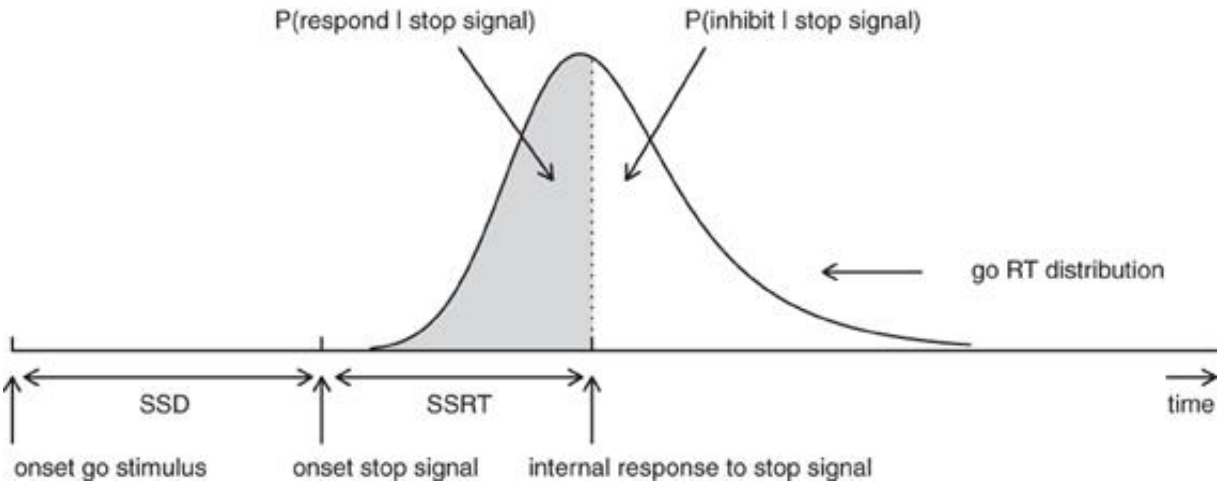

Figure 1. Graphical representation of the Horse Race model. Given an individual reaction time (RT) distribution, the stop-signal reaction time (SSRT) depicts the time from onset of a stop-signal to a given probability (P) of successfully stopping. The stop-signal delay (SSD) is the time from the initial go stimulus to the stop-signal. The SSRT when P=50% successful stopping, serves as a measure of inhibition efficiency. Illustration courtesy of Matzke, Dolan, Logan, Brown and Wagenmakers (2013).

Neural underpinnings

The GNG and the SST has been used in combination with a wide range of methods, such as; functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), electroencephalography (EEG), transcranial Direct Current Stimulation (tDCS), transcranial magnetic stimulation (TMS), and lesions studies. Based on a systematic review of neuroimaging and lesion studies, Aron and colleagues (2004) argues that the rIFG is the most likely neural basis for response inhibition. Ridderinkhof and colleagues (2004) reviewed monkey and human studies and targeted among others, venterolateral prefrontal cortex (including rIFG) as a likely candidate. A meta-study by Swick, Ashley and Turken (2011) performed a meta-analysis based on 66 fMRI studies of GNG and SST, and found that the major clusters of activation was located in the right anterior insula (rAI) and the pre-supplementary motor area (pre-SMA). However, the researchers noted that the rAI and rIFG activity in these studies might be misinterpreted concerning their origin, as areas of close proximity (i.e. rIFG and rAI) might be confounded due to pre-processing steps such as spatial smoothing. Accordingly, a follow up review by Aron and colleagues (2014) supported the role of rIFG in response inhibition. Moreover, the researchers argued that prolonged reaction times in general is a hallmark of insula lesions, thus confounding the right insula hypothesis proposed by Swick et al (2011). The findings from the reviews of Aron and co-workers (2004, 2007, 2011, 2014) strongly argue in favor of the proposed role of rIFG in response inhibition. They further argue that response inhibition is mediated through a network

including the rIFG, sub thalamic nucleus (STN) and the pre-SMA. According to this account, pre-SMA prepares the network for inhibition action and the rIFG implements inhibition by projecting signals to the STN which suppresses thalamocortical output, in turn blocking execution of the go response (Aron & Poldrack, 2006; Ray et al., 2009).

However, studies using the GNG find activations bilaterally and even left lateralized. Rubia et al (2001) did a conjunction analysis of fMRI results from 15 participants doing two different GNG tasks and three different SSTs. Results indicated that left inferior frontal gyrus (lIFG) was more activated in the GNG task than in the SST, while higher activations in the rIFG was demonstrated in the SST. Swick et al (2008) tested participants with lIFG centered lesions and healthy controls on the GNG task. They found that performance was significantly reduced in the patient group compared to controls. In a recent fMRI study, Steele and colleagues (2013) found bilateral IFG activity in participants performing the GNG task (N = 102). The lIFG-GNG association has also been identified in a developmental cohort study, correlating age and GNG task performance with cortical areas (Tamm, Menon, & Reiss, 2002).

While both SST and GNG task are used to measure response inhibition, SST is regarded as more valid (Verbruggen & Logan, 2008). It is argued that the GNG involves responding to two or more different response sets (where one is associated with no response), thus the neural activity associated with GNG task performance might be confounded with activity reflecting response selection (Mostofsky & Simmonds, 2008). Given the more unilateralized results from studies using the SST compared to the GNG, there appears to be emerging general consensus that the rIFG, rather than the lIFG, may be the principle component for initiating response inhibition. However, the view that the rIFG mediates response inhibition has been challenged by findings associating rIFG activity with other cognitive functions, such as attentional reorienting.

Attention reorienting and rIFG

Hampshire and colleagues (2010) suggests a more general purpose for rIFG as the rIFG has been implicated in a diverse range of processes, such as response conflict, working memory, and perceptual difficulty (see Duncan & Owen, 2000; Miller & Cohen, 2001). Importantly, rIFG activity has been associated with target detection, which is in accordance with the attentional reorienting model of Corbetta and Shulman (2002). Hampshire et al (2010) argued that as rIFG is central in attention, and that target detection and reorienting might explain the diverse range of rIFG associations, including response inhibition. They

investigated this hypothesis in an fMRI study where participants were tested with three versions of the SST. Each version had a different instruction on how to respond to the stop-signal; counting the number of signals; key press (dependent on target); and to inhibit the go response. Consistent with previous findings, results revealed increased rIFG activity in stop-signal trials compared to go trials. However, and inconsistent with the proposed purely inhibitory role of rIFG, the increased activation on stop-signal trials was independent of whether the participants successfully stopped or not, and whether participants were instructed to stop at this signal or not. Hampshire and colleagues (2010) argued that due the role of the stop-signal stimulus as a distractor or response associated target, these results support the notion that rIFG is not necessarily responsible for response inhibition per se, but for detection of unexpected targets like the stop-signal in the SST. The researchers further argued that pre-SMA is a more likely candidate (see also Sharp et al., 2010). Thus, rIFG activity thought to reflect inhibition in earlier studies may in fact be confounded with attentional capture and reorienting.

In their visual attention model, Corbetta and Shulman (2002) propose two main cortical networks of attentional control; a dorsal and a right hemispheric ventral stream. The dorsal stream is responsible for orienting and sustaining attentional resources towards behaviorally relevant targets, while the ventral stream is responsible for disengaging and relocating attention to new or sudden relevant stimuli. In this model, rIFG is hypothesized to act as the "go" area for the ventral stream, in such a way that low levels of rIFG activity keeps our attention focused and less responsive to distracting irrelevant stimuli. High activity in rIFG on the other hand, signals that new stimuli are more behaviorally relevant, either cued by change of internal goal set and behavioral plan, or by unexpected potentially important stimuli located outside our current focus of attention (see also Corbetta, Patel, & Shulman, 2008). In such a scenario, rIFG may inform about a change in stimuli, such as detecting a different target (GNG) or an abort signal (SST), and thus signal a network reset (Corbetta et al., 2008; Sara, 2009). The more general role of rIFG as a network reset area, rather than a specific area for inhibition may offer an explanation to the rIFG activity observed in the study of Hampshire et al (2010).

However, Hampshire and colleagues (2010) suggest that two functionally distinct sub-regions of the rIFG might exist; one region being involved in attention while another region being involved in inhibition. The close proximity of these two regions may have led to overlapping fMRI indicated brain activity in earlier studies. Accordingly, in a recent meta-

analysis based on 87 fMRI studies of response inhibition and attention reorienting tasks, Levy and Wagner (2011) found that attentional shifting and motor response inhibition could be attributed to two distinct areas of the posterior part of rIFG pars opercularis; a more inferior part supporting inhibition, and a more superior part close to the inferior frontal junction supporting attention (figure 2). In addition, the review of Aron and colleagues (2014) argue that the study of Hampshire et al (2010) and similar investigations still measure inhibition, albeit more weakly. They argue that even though participants are not stopping, they slow down or partially inhibit their responses when faced with salient, infrequent or unexpected visual stimuli, and that the success of inhibition is dependent on the degree of synchronous activation of the rIFG/pre-SMA/STN network.

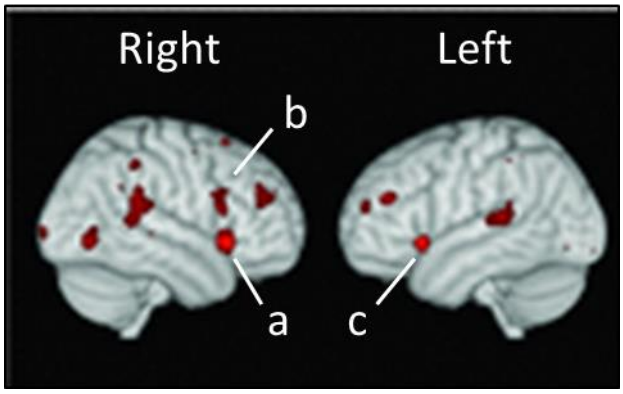

Figure 2. Cortical areas activated in a stop signal task for successful stops contrasted against unsuccessful stops. The areas of interest are; (a) the inferior subregion of right inferior frontal gyrus (IFG) pars opercularis; (b) the superior subregion of right IFG pars opercularis; (c) the inferior subregion of left IFG. (a) is implicated in response inhibition, (b) in attentional reorienting, (c) in response selection. Courtesy of Levy and Wagner (2011)

Taken together, attentional models may explain the association between rIFG activations on response inhibition tasks reported in earlier studies. However, simply measuring individual performance in reorienting tasks and inhibition tasks and correlating them with individual differences in rIFG activation levels might not be sufficient to distinguish the two conflicting explanations and in turn rule out one on behalf of the other. One way to experimentally resolve the issue of whether this region is particularly responsible for response inhibition is to use a causal rather than a correlational method, such as neurofeedback (NF).

Neurofeedback

Neurofeedback is a method that allows participants to directly or indirectly assess their measured neural activity in such a way that through training, he or she is granted some amount of control over the output. Since the 1960s, EEG has been used in NF training where participants learn to influence and control their brainwave rhythms. Within the field of psychiatry, EEG NF has been used as a therapeutic tool in regards to among others, ADHD,

depression, seizures and epilepsy (Hammond, 2007, 2008). Interest in NF as an experimental method has also begun to emerge within the field of neuroscience. However, while EEG has prominent temporal resolution advantages, spatial resolution is a disadvantage. Considering the two-part distinction of the rIFG pars opercularis subdivisions and their different functions proposed by Levy and Wagner (2011), experimental methods such as direct electrical stimulation (DES), EEG NF, TMS and TDCS might be either to invasive (DES) or insufficient in terms of spatial resolution in order to investigate the specific question at hand. Conversely, fMRI has the advantage of higher spatial resolution and minimal invasiveness compared to the fore mentioned methods, making it a promising method for NF.

Advances in scanner architecture and computing power have made it possible to perform real-time fMRI analyses (rt-fMRI) with time lag of less than a second, including scanner repetition time (TR), and an increasing amounts of studies have successfully employed rt-fMRI as a NF device (for reviews, see deCharms, 2008; Sitaram et al., 2007; Sulzer et al., 2013). In a typical rt-fMRI NF training session, a participant is asked to focus on a certain type of visually presented stimulus (e.g., a green disc) and try to increase the size of it. The size of the stimulus is reflected by the ongoing hemodynamic response recorded and analyzed in real-time from a brain region of interest (ROI). By trial and error, the participant eventually learns how to control indicated brain activity, even though the cognitive processes required for increased activation is in many cases on an unconscious level (e.g. Shibata, Watanabe, Sasaki, & Kawato, 2011). Research findings has demonstrated that rt-fMRI NF training enables participants to modulate their own neural activation in both cortical (Weiskopf, 2012) and subcortical areas (Johnston, Boehm, Healy, Goebel, & Linden, 2010) as indexed by concomitant changes in the blood oxygen level dependent (BOLD) signal.

While rt-fMRI NF has not been employed on the topic of response inhibition, one study report successful NF training on a more anterior region of rIFG; pars triangularis (Rota et al., 2009). In addition, several studies using other methods suggest that increased inhibition efficiency is possible by modulation of rIFG activity. Sasaki, Gemba and Tsujimoto (1989) used DES on rIFG equivalent neurons in rhesus monkeys, while they performed the GNG task. Results revealed that electric stimulation of these neurons was associated with enhanced inhibition performance on the GNG-task. In addition, in a recent study by Wessel and colleagues (2013), DES was employed in the rIFG of four participants scheduled for open brain epilepsy surgery. The results showed an increase in slowing and stopping capabilities in a modified SST. Jacobson, Javitt and Lavidor (2011) applied focal tDCS on the rIFG and

results indicated that anodal stimulation, increasing neural activity, resulted in lower SSRTs on an SST. However, these methods are either too invasive or have insufficient spatial resolution to investigate the inferior and superior subdivisions of rIFG pars opercularis. Thus, given the spatial resolution and experimental nature of rt-fMRI NF training it might be a useful, non-invasive approach to investigate the suggested role of rIFG in response inhibition further.

Present Project

The main goal of this project was to experimentally test the proposed link between the rIFG and motor response inhibition. By measuring performance on a response inhibition task pre vs. post rt-fMRI NF training on the inferior subregion of rIFG pars opercularis, any behavioral changes can be causally related to the cortical area a participant received NF on. A SST (see Logan, 1994) was used to measure participants' ability to withhold a response on trials where a stop-signal is presented. Inhibition efficiency was assessed using stop-signal reaction time (SSRT), a measure computed by subtracting the delay between go stimulus and stop-signal presentation, stop-signal delay (SSD), from mean reaction time (RT). If, as suggested by Hampshire et al (2010), the rIFG is involved in attention reorienting alone, NF training on the inferior subdivision of rIFG pars opercularis should predict task performance on an attentional reorienting task in addition to the SST. Hence, supplementary to the SST, a modified Posner cueing task (PCT) (see Posner, Snyder, & Davidson, 1980) was used to investigate the role of rIFG on attention reorienting. Here, participants respond to targets that may appear in 2 different spatial locations on a computer display. The targets' spatial locations are validly or invalidly cued by endogenous semantic cues appearing at a fixed location of the display. In cue invalid trials, participants are required to quickly reallocate their attention towards a new spatial location from what was initially cued. Typical findings from studies using the PCT show that reaction times are longer on cue invalid trials compared to cue valid trials (e.g. Bayliss, Pellegrino, & Tipper, 2005; Doricchi, Macci, Silvetti, & Macaluso, 2010). The increase in RTs from valid to invalid trials is a measure of cost of reorienting, and will hereby be referred to as the cost of reorienting component (CORC). The PCT has also been previously associated with rIFG activity (e.g. Peelen, Heslenfeld, & Theeuwes, 2004; Vossel, Thiel, & Fink, 2006). To further validate the role of the right lateralized IFG specifically in response inhibition, a second group received NF training on the lIFG. In addition, previous research has indicated that there are gender differences in results in the neural correlates of response inhibition (see Li et al., 2009; Li, Huang, Constable, &

Sinha, 2006), and the PCT (see Merritt et al., 2007). There have also been indicated gender differences in the effect of EEG NF training (Ibric, Dragomirescu, & Hudspeth, 2009) and in cortical neuroplasticity (Kuo, Paulus, & Nitsche, 2006) possibly affecting rt-fMRI NR training. Due to these differences, gender was included as a between group variable, however no gender specific effects were expected on the particular measures of interest (SSRT, CORC).

Hypothesis and Predictions

If the inferior subdivision of rIFG pars opercularis is involved in response inhibition, and not attention reorienting processes, the group receiving NF on the inferior subdivision of the rIFG pars opercularis (hereby referred to as the rIFG group) should result in an improved task performance on the SST (i.e. lower SSRTs), while no such effects should be observable on PCT task performance. Conversely, if the rIFG is involved in attention reorienting, successful NF training for the rIFG group should result in enhanced performance on both tasks (i.e., shorter SSRTs on the SST, and decreased CORC on the PCT). Moreover, if inhibition is specifically right lateralized, any effects on post-training task performance should be observed for the rIFG group, as compared to the group receiving NF training on the inferior subdivision of the lIFG pars operculais (hereby referred to as the lIFG group). See table 1 for summary and operationalization of predictions.

Table 1

Summary of Predictions

Prediction	Type	Independent	Where	Effect	Dependent
1a	Behavioral	NF training	I.S. rIFG pars opercularis	Increases	SSRT
1b	Behavioral	NF training	I.S. rIFG pars opercularis	Increases	SSRT & CORC
2a	Neurofeedback	NF t-value		Correlates with	BOLD signal
2b	Neurofeedback	NF t-value		Predicts	SSRT
2c	Neurofeedback	NF t-value		Predicts	SSRT & CORC
3a	Brain imaging	Activity maps	Left & Right I.S. IFG pars opercularis	Reflects	rIFG & lIFG group
3b	Brain imaging	BOLD signal	I.S. rIFG pars opercularis	Predicts	SSRT
3c	Brain imaging	BOLD signal	I.S. rIFG pars opercularis	Predicts	SSRT & CORC
4	Gender differences	Gender		No difference	SSRT & CORC

Note. Prediction table for later reference. If the right inferior frontal gyrus (rIFG) is mainly responsible for inhibition, it is predicted 1a, 2b, 3b. If the rIFG is mainly responsible for attention reorienting, it is predicted 1b, 2c, 3c. Prediction 2a, 3a and 4 are general.
NF; Neurofeedback. *T-value*; t-value associated with NF training performance. *I.S.*; Inferior subregion. *r*; right. *l*; left. *IFG*; inferior frontal gyrus. *SSRT*; stop signal reaction time (Stop signal task). *CORC*; cost of reorienting component (Posner cueing task). *BOLD*; Blood oxygen level dependent.

Methods

Participants

Thirty volunteer participants ($N_{females}$ = 13), recruited from the student population of the University of Oslo, took part in the study ($Mean_{age}$ = 23.8, SD_{age} = 5.8). Inclusion criteria for participating in the study was; normal or corrected to normal vision, no reported earlier head trauma, and no current mental state that may affect performance (queried by self-report). Participants were randomly assigned to either the rIFG group or the lIFG group, matched on gender (rIFG group: $Mean_{age}$ = 24, SD_{age} = 7.1; lIFG group: $Mean_{age}$ = 23.6, SD_{age} = 4.3). Participants were instructed to abstain from nicotine or caffeine intake for at least 1 hour before the experiment took place, and during the testing sessions. In addition, participants were instructed to withhold all use of alcohol during the two days the study lasted. After receiving information about the study, each participant gave his or her written informed consent. All procedures conformed to the national and institutional guidelines of the Helsinki Declaration. As compensation for his or her participation, each participant received NOK 400 after completion of the second testing session.

Study Design

The design was a 2 (*Session*; pretest, posttest) x 2 (*NF-Group*; rIFG, lIFG) x 2 (*Gender*; males, females) factorial design, with Session as within-subject factor, and Group and Gender as between-subjects factors.

Setup

Behavioral tasks. The machine used for the behavioral task was a Dell Precision T7600 with 2x Intel Xeon 2.4 ghz processors and 6gb ram, running Windows 7 Professional 64 bit. The SST was run on MatLab (R2013b 64-bit) with the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997), using a BenQ screen with resolution of 1280x720 pixels and 60 hz refresh rate. Participants were situated 40 cm from the screen. The PCT was run on E-Prime (2.02), with a screen resolution of 1200x800 pixels. Participants were situated 50 cm from the screen. Responses were delivered on a standard QWERTY keyboard.

Neuroimaging. Scanning was performed on a 3 Tesla Philips Achieva whole body MR scanner, equipped with an 8-channel Philips SENSE head coil (Philips Medical Systems, Best, the Netherland). For the real-time NF training sessions, a BOLD sensitive T2* echo-planar imaging sequence (TR 54 ms, TE 30 ms, FOV 192 x 192 x 45, flip angle 80°, serial acquisition) with 15 slices and a voxel sixe of 3x3x3 mm was used, for a total volume dynamic scan time of 810 ms. One session consisted of 380 volumes, and lasted 5 minutes and 40 seconds. The first ten volumes were discarded from all analyses to allow for MR signal equilibrium. For online motion correction of the NF training functional images in real-time, a 10-volume NF training scan was recorded for registration, where the 9 first volumes were excluded, to avoid saturation effects. In order to guide the drawing of ROIs an anatomical partial FOV T1 weighted image (TR 5.5 ms, TE 2.5 ms; FOV 192x192x45, flip angle 8°) with voxel size 1.5x1.5x1.5 mm and 30 slices was acquired. For offline registration of the functional data, an anatomical T1 weighted image was acquired (TR 6.6 ms, TE 3.1 ms; FOV 256x256x204, flip angle 8°) with voxel size 1x1x1.2 and 170 slices.

Neurofeedback. The NF paradigm was implemented using E-Prime (2.02)), and presented on a MR-compatible LCD sceen (NNL LCD Monitor®, NordicNeuroLab, Bergen, Norway) placed behind the scanner bore, and participants viewed the screen through a mirror mounted on the coil, resulting in an effective viewing distance of 1.2 meters and a field of view measuring 32°. Screen resolution was set to 1920x1080 at 60 Hz refresh rate. The computer handling the NF stimuli was the same as in the behavioral tasks (see setup; behavioral tasks).

The XTC computer handling the retrieving and further distribution of the online reconstructed functional images was a HP Z600 Workstation with 2x Intel Xeon processors of 2.53 ghz and 6 gb ram, running Windows 7 Professional 64 bit. Images were grabbed using Corbadatadumper (1.1). The AFNI computer handling the online analysis was a Dell Precision T7600 with 4x Intel Xeon processors of 2.4 ghz and7.7 gb ram, running Debian Linux with Gnome (3.4.2). The online analyses were run in AFNI (07_2013)(Cox, 1996) using the afni_proc.py processing stream and a range of custom scripts. For more information on the information flow, see figure 3 and appendix; information flow. For report of piloting, see appendix; Neurofeedback Pilot.

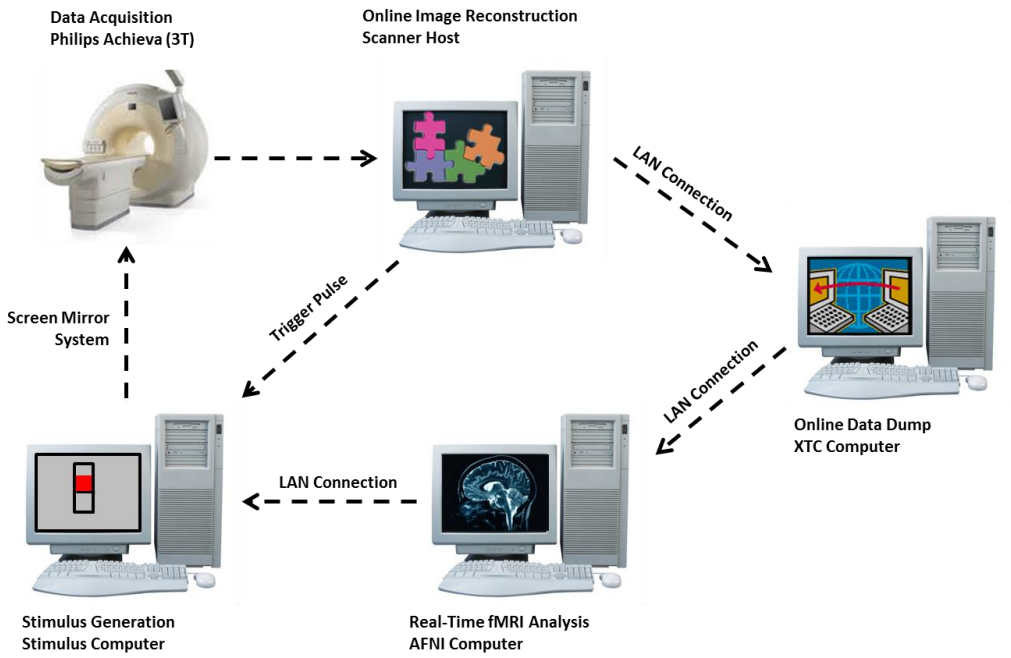

Figure 3. The real-time Neurofeedback Training Setup. Dynamic images are acquired in the *scanner* and reconstructed in the *Scanner host* computer. The *XTC* computer grabs the images and sends them to the *AFNI* computer for real-time analysis. The result of the analysis are sent to the *Stimulus* computer for display in the *Scanner* through a screen and mirror system. The *Stimulus* computer is triggered by the *Scanner host* computer every *scanner* repetition time (TR). For more details read; methods, Neurofeedback; and appendix, information flow.

Tasks

Stop-signal task. Motor Response Inhibition was measured using the Stop-It program (Verbruggen, Logan, & Stevens, 2008) and run on The SST consisted of five blocks, where the first served as training. Each block consisted of 72 trials resulting in a total of 320 trials, and a total running time of 13 minutes. A trial could either be a go-signal trial or a stop-signal trial, which were randomized within each block (75% and 25% of total trials, respectively). Between each block, participants received feedback on their performance. The feedback, presented for 15 seconds on the computer screen, consisted of average RT and accuracy on go-signal and stop-signal trials on the previous block.

On go-signal trials, a fixation cross was presented for 500 ms (1°), followed by presentation of the task stimulus for 1500 ms. The stimulus could either be a square (2,8°) or a diamond (2.8°). Stimuli were white presented in the center of a black screen. Subjects were instructed to respond to the target identity as fast and accurately as possible by pressing “c”, if the target was a square, or “m”, if the target was a diamond, using their left and right middle fingers, respectively. Responses needed to be made during the target stimulus presentation

time. Any responses given after target stimulus offset were counted as errors. Stop-signal trials were identical to the go-signal trials with one exception; a stop-signal was presented after target-display onset to signal to the participant that the planned response should be withheld. The SSD, or the time (in ms) between target onset and the stop-signal, was adjusted trial-by-trial using a staircase procedure from an initial value of 250 ms. For each successful response inhibition on a stop-signal trial, SSD increased by 50 ms. Conversely, SSD was decreased by 50 ms when the participant failed to inhibit his or her response. This staircase procedure ensures that each participant's mean accuracy level on stop-signal trials approximates 50%, recommended when using the integration method (see preprocessing & analysis). Participants were naive about the staircase procedure (see visual setup in figure 4).

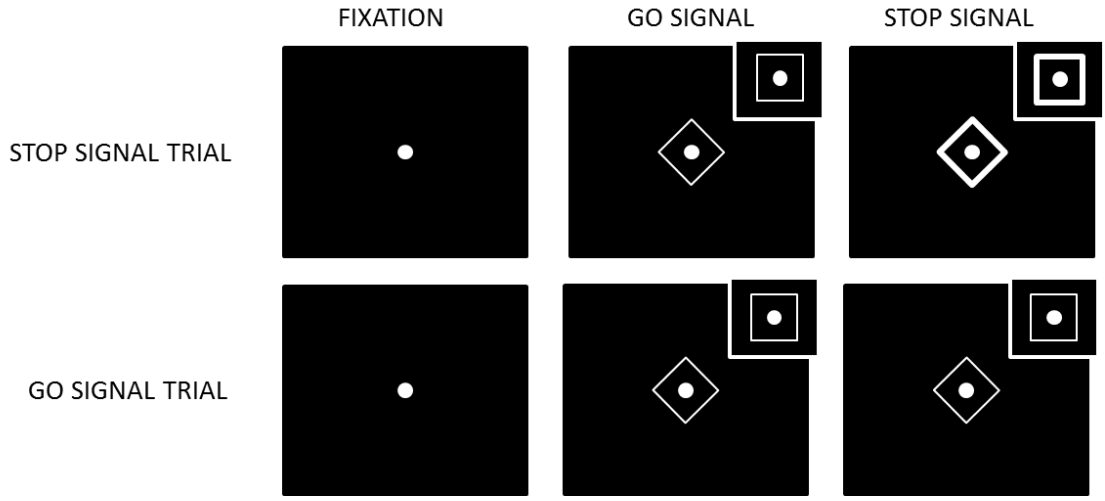

Figure 4. Overview of the stop signal task. In the go trial a fixation point is presented for 500 ms, followed by presentation of target stimulus for 1500 ms. Participants were instructed to indicate whether the target was a diamond or a square (as seen in the top right corner). In a stop signal trial, the target was presented for a variable time before the stop signal stimulus was presented. The stop signal was a bolded version of the target stimulus. Participants were instructed to try to withhold their original target response when presented with the stop signal. The time before stop signal appearance was controlled by a staircase procedure, increasing or decreasing based on success or failure in stopping.

Posner Cueing task. CORC was measured using a custom PCT implemented in E-Prime (Version 2.01). The PCT consisted of one training block and one experimental block with total running time of 13 minutes, consisting of 25 and 160 trials respectively. Subjects were presented with either the letter "A" or "L" (Font name: Courier, Font size: x), and their task was to respond to the identity of the target letter using the keys A or L on a keyboard as fast and accurately as possible. At the beginning of each trial, a centered fixation cross (1.7°)

was presented for 750 ms, followed by a centered cue presented for 300 ms. The cue could be either "up" – ["opp" in Norwegian] (5.1°), "down" – ["ned" in Norwegian] (5.1°) or neutral – ["(+)"] (4°). The target could be presented in two locations, identified by two squares (4.5°) located superior and inferior to the centered cue (11.4° center to center). All stimuli were black and presented on a grey screen. A trial could either be neutral, valid or invalid, randomized within each block (25%, 50%, 25% of total trials, respectively). A neutral trial (specified by the neutral cue) indicated a 50% chance of target appearance location. A valid trial (specified by either the up or down cue) indicated correctly target appearance location, while an invalid trial incorrectly indicated target appearance location. After a random delay ranging from 500 ms to 1300 ms following a uniform distribution with 5 intervals, the target was presented at one of the locations for 1000 ms.

Participants were instructed to answer as fast and accurately as possible while always fixating on the middle cross and using their attention or peripheral vision to detect targets (see visual setup in figure x, and for pilot data see appendix; Posner Cueing Task Pilot).

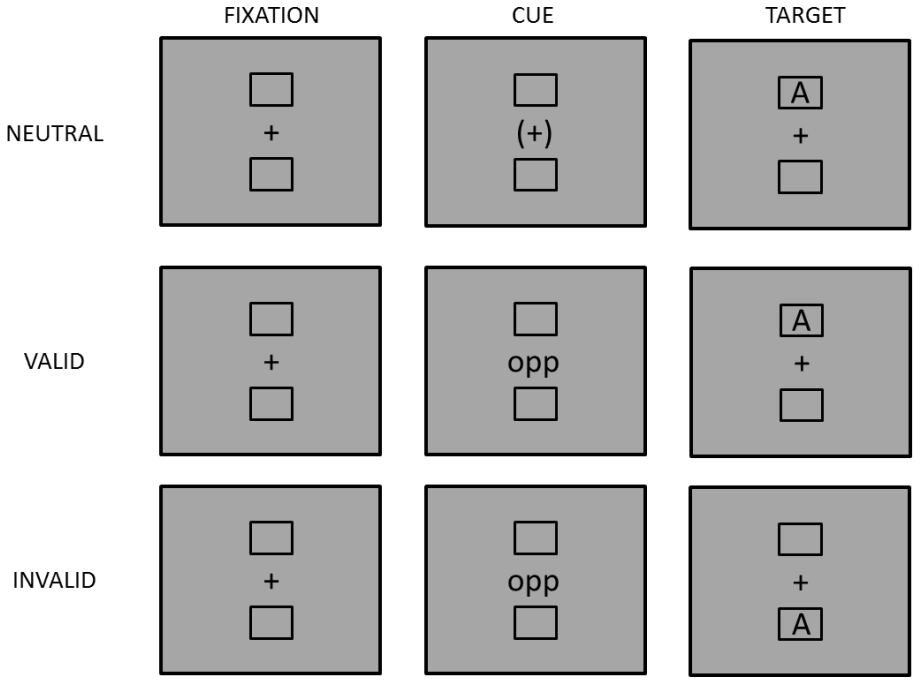

Figure 5. Overview of the Posner Cueing Task. A fixation cross is presented for 750 ms, followed by a semantic cue indicating target location, for 300 ms. The cue could be either; (+) [neutral], offering no indication of target appearance location; *opp* ["up" in Norwegian] indicating target appearance in the superior boundary box; *ned* ["down" in Norwegian] indicating target appearance in the inferior boundary box. The target was presented for 1000 ms after a variable delay of 500 ms to 1300 ms (uniform distribution, 5 levels). In valid trials, the target was presented at the cued location. In invalid trials, the target was presented at the un-cued location. Participants were instructed to indicate the target letter (A, L) with the keyboard.

Neurofeedback task. One session of NF training consisted of a baseline block, and eight alternating rest and up-regulation blocks. The baseline block consisted of a black rectangle (12.3°) where average BOLD signal was measured. A rest block consisted of a black rectangle with a dynamic red bar in the middle. The size and direction of the red bar was controlled by real-time information of the BOLD signal in the target ROI and reference ROI (see below). The rest block was indicated with a blue "> <" on each side of the black rectangle. The up-regulation was identical to the rest block, except for a blue "^ ^" on each side of the black rectangle. Block duration was equivalent to 40 TRs[1] (approximately 32 seconds). Between each block, a fixation cross was presented for one TR.

Participants were instructed to try to increase the size of the red styled thermometer bar in the up-regulation conditions, and relax during the baseline and rest conditions. The instructions did not require the participants to perform any specific type of cognitive strategy, instead the participants were encouraged to experiment with different strategies. Participants were informed that due to the intrinsic lag of the hemodynamic response, the feedback would not be immediate. Participants were also instructed that habituation may occur during a block, and that they might try to take brief pauses (2-3 seconds) to further increase chance of success. Participants were also instructed to change their relaxation strategies after a few sessions if they felt they didn't manage to up-regulate. Relaxation strategies were told to be in the form of relaxing imagery.

The online BOLD measurements presented to the participant were computed from two ROIs, target and reference. The target ROI (spherical, radius 7mm) was manually placed in the inferior sub-region of either the right or the left IFG pars opercularis depending on group. Ten reference ROIs (spherical, 7mm) were manually placed in the same axial plane as the target ROI (see figure 6). The large number of reference ROIs was included to mitigate universal scanner drift, global changes in blood diffusion and supply, and movement induced signal change. Mean signal from the target and reference ROIs were aggregated and compared on each TR (see equation 1)

During the baseline condition of the NF-training task, average BOLD-signal for the first 30 TRs were compared between the target and reference ROIs in order to establish a baseline relative difference. During the rest and up-regulation conditions, the result of the comparison between target and reference ROIs for each TR was aggregated into a rolling average of 2. The rolling average was compared to baseline as a percent-wise difference, and

[1] For simplicity; TR will herby refer to as the total volume dynamic acquisition time, 810 ms.

then presented on the stimulus screen to the participant in the form of a red graph. The red graph represented relative percent-wise difference between baseline and the rolling average. Each integer increase in percent-wise difference was equal to 50 pixels on the screen (see visual setup in figure 7).

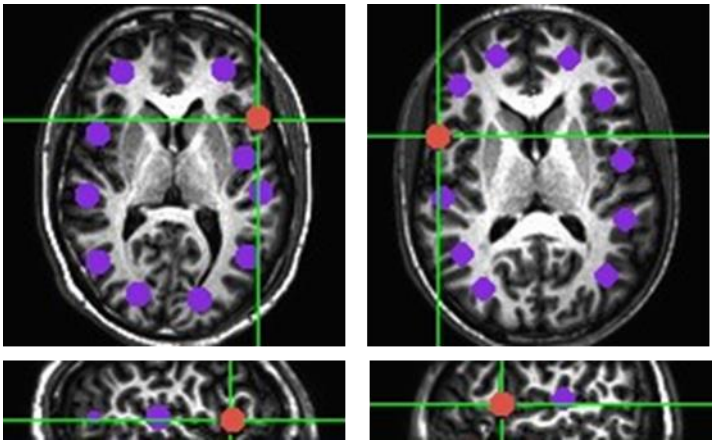

Figure 6. Sample of online defined region of interests (ROI) for use during the Neurofeedback training task. Pictures show two individual participants' defined ROIs. One target ROI (orange) and ten reference ROIs (purple). ROIs are centered on the left or right inferior subregion of the inferior frontal gyrus (rIFG) pars opercularis, depending on group.

$$\frac{TAR_{TR-1} + TAR_{TR} * 50}{\sum_{TR=0}^{n=30} \frac{TAR_{TR}}{n}} - \frac{REF_{TR-1} + REF_{TR} * 50}{\sum_{TR=0}^{n=30} \frac{REF_{TR}}{n}} - 200$$

Equation 1. Algorithm for calculating the difference between mean voxel signal strength in a target (TAR) and reference (REF) region of intereset (ROI). The equation returns a percent value indicating the relative difference from baseline in target ROI vs. reference ROI.
Legend: TR; the current number of scanner repetition times.
Moving average; $TAR_{TR-1} + TAR_{TR}$ Target baseline; $\sum_{TR=0}^{n=30} \frac{TAR_{TR}}{n}$

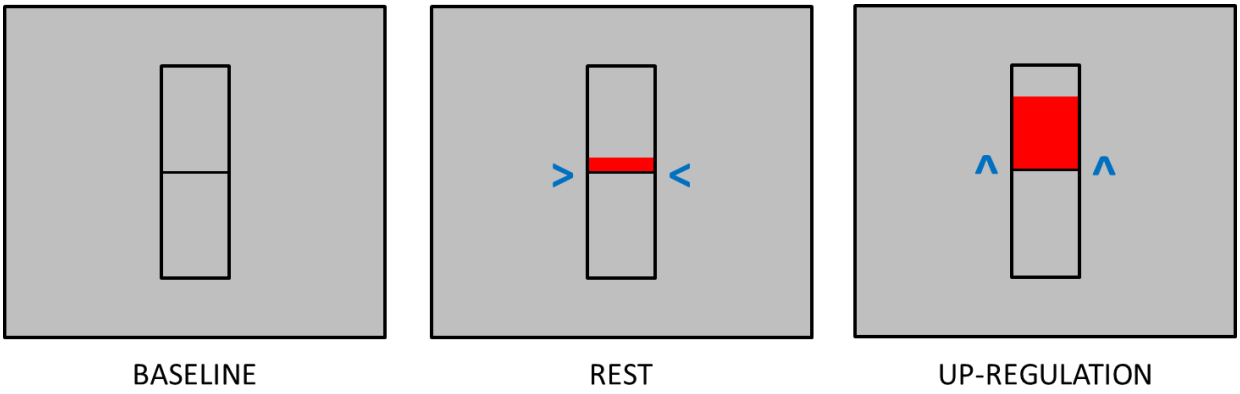

Figure 7. Overview of the Neurofeedback Training Task. The baseline trial was presented at acquisition start, followed by a rest trial and an up-regulation trial. The last six trials consisted of alternating rest and up-regulation. Each trial lasted for 40 scanner repetition times (TR), approximately 32 seconds, and in-between each trial a fixation cross was presented for 810 ms (1 TR). Participants were instructed to increase the size of the red bar in the up-regulation trials, and relax during baseline and rest trials. The size of the red bar was controlled by the difference in online measured hemodynamic response in a right inferior frontal gyrus region of interest, and a larger reference region of interest.

Procedure

The experiment took place over two consecutive days. On the first day, all participants were presented with an information and consent form. The areas they could receive feedback from were not disclosed. Participants performed the SST first and then the PCT. After the behavioral tasks, participants were positioned in the scanner and cushioned with foam rubber to decrease movement. The scanning session consisted of a survey scan, a partial FOV fMRI scan for online motion correction, a partial FOV structural MRI scan for drawing ROIs, a structural MRI scan for offline registration, and five NF training sessions. Between each NF session participants were encouraged verbally to "continue the good performance". The second part of the study took place 24 hours after the starting time of the first part. The second part started with the scanning session, which consisted of a survey scan, a partial FOV fMRI scan, a partial FOV structural MRI scan, five NF training sessions, and a structural MRI scan. The second day of study ended with a re-test on the behavioral tasks; first the SST and then the PCT.

Preprocessing and analysis

Neurofeedback. Data from the NF training task, as collected by the rt-fMRI setup (see methods; neurofeedback), was aggregated by calculating the median for each session for each participant for each condition (up-regulation, rest). Additionally, the first 10, as well as the last 5 TR's were excluded from the data analysis to avoid bleed-over and expectation effects, respectively (resulting in a total of 25 TRs for analysis). As an indication of whether a participant consistently managed to up-regulate his or her own hemodynamic response, a paired one-tailed student's t-test for each participant was performed between the rest condition and the up regulation condition (see Koush, Zvyagintsev, Dyck, Mathiak, & Mathiak, 2012; Linden et al., 2012). The associated t-value was stored for further analysis as a covariate and as a proxy of success in the NF training task. The measured difference between up-regulation and rest was calculated for each participant. To investigate whether participants managed to consistently up-regulate and also if practice resulted in higher up-regulation, a repeated measures analysis of variance (ANOVA) was performed on the difference scores, with session (1-10) as a within subjects variable, and group and gender as between subjects variables. A main effect of session was expected to indicate learning, while a significant intercept was expected to indicate consistent up-regulation.

Stop Signal Task. SSRTs were computed from the SST data in accordance with the integration method (see Verbruggen & Logan, 2009) using an inbuilt Stop-It script (Verbruggen & Logan, 2008). The integration method computes the SSRT by using the average go-signal RT and the SSD at the percentile of the mean P|successful stop, where P|0.5 equals median SSD. Data were excluded using the lenient method (Congdon et al., 2012) with the following criteria; SSRT below 50, P|stop at stop-signal over 0.7 or below 0.3, accuracy go-signal under 0.6. Removed scores were labeled missing. The lenient method was followed by a 3 times inter quartile range (IQR) outlier detection algorithm over each group and session. Due to low number of participants the scores marked by the 3 IQT algorithm was replaced by the mean minus (if lower end outlier) or plus (if higher end outlier) 2 times standard deviation (SD) (Andy Field, 2009, p. 183).

To investigate whether participants in the rIFG group showed the predicted improvement in SST performance as a result of the NF training (1a), an analysis of covariance (ANCOVA) on the SSRTs was performed, with sessions (pre, post) as within subjects

variable, and group (rIFG, lIFG) and gender (males, females) as between subjects variables. The NF training associated t-value was used as a covariate to account for individual within-group differences that may have been caused by the NF training. A significant interaction between group and session was expected to indicate a decrease in SSRTs caused by the NF-training for the rIFG group. It was also expected according to predictions (2b) that the NF training associated t-value would be negatively associated with measured increase in SSRTs over sessions for the rIFG group, indicating that improved up-regulation (higher t-value) would predict decreased SSRTs (improved response inhibition efficiency).

Posner Cueing Task. The PCT data were aggregated by the median of each session for each cue type condition (invalid, neutral, valid). The CORC was calculated by subtracting valid cue type RTs from invalid cue type RTs. The CORC were analyzed using the 3 IQT algorithm over each group and session. Due to low number of participants the scores marked by the 3 IQT algorithm was replaced by the mean plus/minus 2 times SD.

To investigate the prediction that the rIFG group would improve performance on the PCT as a result of the NF (1b), an ANCOVA on the CORC was performed, with session (pre, post) as within subjects variable, and group (rIFG, lIFG) and gender (males, females) as between subjects variables. The NF-training associated t-value was used as a covariate to account for individual within-group differences that may have been caused by the NF training. A significant interaction effect between group and session was expected to indicate a decrease in CORC caused by the NF-training for the rIFG group. It was also expected according to predictions (2c) that the NF training associated t-value would be negatively associated with a measured increase in SSRTs over sessions for the rIFG group, indicating that improved up-regulation (higher t-value) would predict decreased CORC (improved attentional reorienting).

Neuroimaging. All fMRI data were preprocessed and analyzed using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, version 6.00). The following pre-processing steps were performed; motion correction using FMRIB’s Linear Image Registration Tool (MCFLIRT)(Jenkinson & Smith, 2001); brain extraction using Brain Extraction Tool (BET) (Smith, 2002); spatial smoothing using a Gaussian kernel with 5 mm fill width at half maximum; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, sigma = 100s).

Registration of functional images to MNI standard space (12 degrees of freedom (DOF)) through initial high-res partial FOV structural images (3 DOF) and full FOV structural images (12 DOF), was performed using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001).

The design matrix of the General Linear Model (GLM) contained three explanatory variables of interest plus 12 motion correction parameters. Explanatory variables (EV) of interest were baseline, rest and up regulation, modeled as boxcars spanning each block type, and convolved with a double gamma HRF. Each participant's sessions were analyzed with a first level analysis with the main contrast up-regulation minus rest. Time-series statistical analysis was carried out using FMRIB's Improved Linear Model (FILM) with local autocorrelation correction (M W Woolrich, Ripley, Brady, & Smith, 2001). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = .05$ (Worsley, 2001). The resulting COPE images were then combined in a second level analysis of all sessions for each participant in a fixed effects model, by forcing the random effects variance to zero in FMRIB's Local Analysis of Mixed Effects (FLAME) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Taking into consideration that not all runs necessarily activate similarly, each session was weighted according to the mean difference of rest and up-regulation blocks in that session (see appendix; Weighting test), based on the median NF score calculated from TR 10 to 35 for each block. Last, a third level analysis was run separately for each group (rIFG, lIFG) and gender, using FLAME stage 1 and 2 with automatic outlier detection (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p = .05$ (Worsley, 2001).

According to task design and predictions (3a), it was expected that there would be major clusters of activity in the right or left rIFG depending on target NF training area, and (2a) that activity in the inferior subregion of the rIFG pars opercularis would be positively correlated with the NF-training associated t-value as well as (3b, 3c) predict post training task performance.

Results

Neurofeedback

28 participants completed 10 runs of the NF training, while two participants completed 9 and 6 runs, respectively, due to technical errors during image acquisition. The data violated the assumption of sphericity, thus the Greenhouse Geisser test was reported from the repeated measures ANOVA. There was no significant effect of session, $F(4.31,103.49) = 0.76$, $p = .562$, $\eta^2_p = .377$, indicating contrary to expectation, that there was no overall learning effect. There was however a significant intercept, $F(1,24) = 19.52$, $p < .0001$, $\eta^2_p = .449$, indicating a consistent up-regulation. A follow-up one sample students t-test across groups confirmed this (M=0.32%, SE=0.08), $t(29) = 3.82$, $p < .001$.

Behavioral Results

Stop Signal Task. All participants completed the SST, however two participants were excluded based on the lenient method. One score was marked as an outlier by the 3IQR algorithm, and replaced with the mean plus 2 times SD. Table 2 show SSRTs for rIFG and lIFG groups split between gender and sessions, as well as frequency of improvement on task. The ANCOVA results did not reveal the predicted (1a) interaction effect between group and session, $F(1,23) = 2.45$, $p = .131$, $\eta^2_p = .096$, indicating no effect on response inhibition from NF training between groups. There was however a significant main effect of group, $F(1,23) = 5.88$, $p = .024$, $\eta^2_p = .204$, indicating an overall group difference on performance, and a significant main effect of gender, $F(1,23) = 13.6$, $p = .001$, $\eta^2_p = .372$, indicating an overall gender difference on performance. Given the overall unexpected group and gender differences, two measures were taken to account for within group variance. 1) groups were split by gender in effect making four groups (rIFG males, rIFG females, lIFG males, lIFG females). 2) Given only two levels of session, the difference in SSRTs between pre and post NF training, was computed.

The SSRTs were re-analyzed with group (rIFG males, rIFG females, lIFG males, lIFG females) as a between subjects variable, and the NF training associated t-value as covariate. Results revealed a close to significant main effect of group, $F(3,23) = 2.51$, $p = .084$, $\eta^2_p = .247$, indicating a trend toward group differences on the computed SSRT change. Follow up pairwise comparisons on mean SSRT change revealed that the males in the rIFG group improved significantly compared to females and both genders in the lIFG group, $p < .041$

(figure 8). Linear regression analysis using the NF training associated t-value as predictor of SSRT change resulted in a significant model for the males in the rIFG group, $\beta = 26.13$, $t(7) = 2.49$, $p < .047$, $r^2 = .509$, $F(1, 6) = 6.22$, $p < .047$, but only a close to significant model for the females in the rIFG group, $\beta = -10.84$, $t(6) = -2.3$, $p > .083$, $r^2 = .569$, $F(1, 6) = 5.28$, $p < .083$.

To summarize, the results did not support the initial prediction (1a) regarding the effect of NF training on SST task performance for the rIFG group. However, further investigations revealed that only males in the rIFG group had improved response inhibition efficiency after NF training, and that the NF training associated t-value was a significant predictor for the improvement, although the predictor had a positive relationship, again contrary to the initial prediction (2b). In addition, the results did not support the prediction (4) that there were no gender differences.

Table 2

Summary of Stop Signal Task Performance

Group	Gender	Pre	Post	Change	Frequency
rIFG	Males	199(9,4)	181(11,5)	-24(13,5)	66,7%
	Females	223(13,1)	245(12,8)	22(13,6)	16,7%
lIFG	Males	172(18,4)	193(8,6)	17(20,1)	25%
	Females	193(7,5)	215(10,3)	23(15,1)	28,6%

Note. Measures are the stop signal reaction time (SSRT), in milliseconds, with Standard Error of the Mean in parentheses. Change is the measured post training improvement where negative values indicates reduced SSRTs. Frequency is the fraction of participants who showed improved task performance.

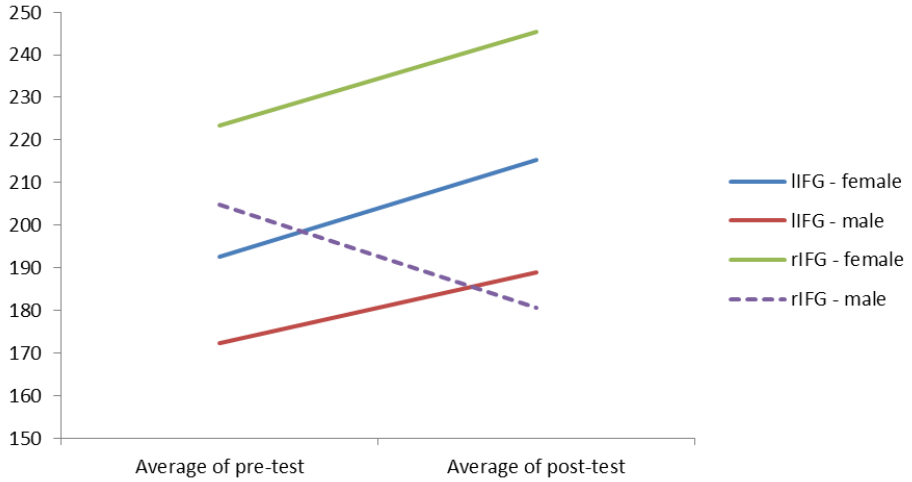

Figure 8. Difference in Stop Signal Reaction Times (SSRT), in milliseconds, pre and post Neurofeedback (NF) training for the stop signal task. The SSRTs are shown for each group and each gender. lIFG; The group receiving NF training on the inferior subregion of the left inferior frontal gyrus (lIFG). rIFG; The group receiving NF training on the inferior subregion of the right inferior frontal gyrus (rIFG).

Posner Cueing Task. All participants completed the PCT, however two scores were marked as an outlier by the 3IQR algorithm and replaced with the mean plus 2 times SD. Table 3 shows the CORC for the rIFG and lIFG group, split between gender and sessions, as well as frequency of improvement. The ANCOVA revealed a significant interaction effect between session and group, $F(1,25) = 4.42$, $p = .046$, $\eta^2_p = .15$, indicating, in line with the initial prediction (1b) that one of the groups differed in CORC after NF training. There was also a significant main effect of session, $F(1,25) = 4.68$, $p = .04$, $\eta^2_p = .158$, indicating overall change in pre to post NF performance. In addition, there was a significant three way interaction effect between session, group and gender, $F(1,25) = 4.26$, $p = .05$, $\eta^2_p = .146$, indicating together with the interaction effect between session and group, that one of the genders in one of the groups showed a significant change in CORC.

Keeping in mind the results of the SST analyses, the same steps were taken to investigate whether the males in the rIFG group showed the same trend in the PCT as the SST. Groups were split by gender making in effect 4 groups (rIFG males, rIFG females, lIFG males, lIFG females), and as with the SSRTs, CORC change between pre and post NF was computed to investigate further. CORC-change was re-analyzed with group (rIFG males, rIFG females, lIFG males, lIFG females) as a between subjects variable, and the NF training associated t-value as a covariate. Results revealed a significant main effect of group, $F(3, 25) = 3.65$, $p = .026$, $\eta^2_p = .305$, indicating group differences on the computed CORC change. Follow up pairwise comparisons on mean CORC change revealed that males in the rIFG group had increased CORC compared to females and both genders in the lIFG group, $p < .031$ (figure 9). Linear regression analysis using the NF-training associated t-value as a predictor of CORC change resulted in no significant model for the males, $p > .464$, or females, $p > .143$ in the rIFG group.

To summarize, the results support the prediction (1b) regarding the effect on NF training on the PCT performance for the rIFG group. However, further investigation revealed that only the males in the rIFG group showed an effect of NF training. Further, they decreased attention reorienting efficiency rather than showing the predicted increase in performance. The NF training associated t-value was not a significant predictor for the measured CORC change, again contrary to the initial prediction (2c). In addition, the results did not support the prediction (4) that there were no gender differences.

Table 3

Summary of Posner Cueing Task Performance

Group	Gender	Pre		Post		Change		Frequency
rIFG	Males	35,4	(6,9)	50,9	(13,2)	15,5	(12,2)	44,5%
	Females	40,1	(12,2)	25,8	(13,8)	-14,2	(7,3)	84,4%
lIFG	Males	39,3	(12,9)	21,4	(6,9)	-17,8	(10,7)	50%
	Females	31,1	(7,1)	15,4	(4,2)	-15,8	(4,5)	100%

Note. Measures are the Cost of Reorienting Component (CORC), in milliseconds, with Standard Error of the Mean in parentheses. Change is the measured post training improvement where negative values indicate reduced CORC. Frequency is the fraction of participants who showed improved task performance.

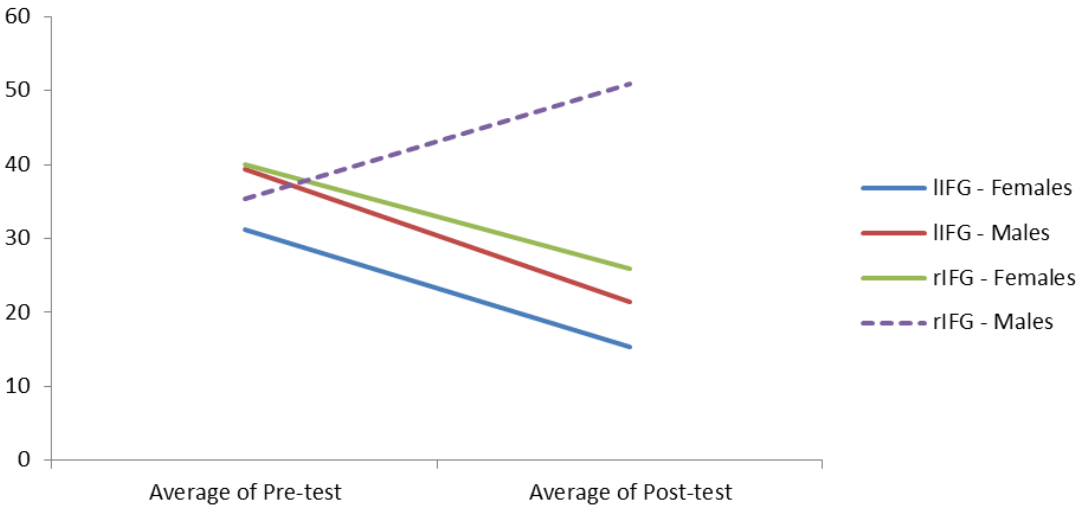

Figure 9. Difference in the cost of reorienting component (CORC), in millisecons, pre and post Neurofeedback (NF) training for the Posner cueing task. The CORC is shown for each group and each gender. lIFG; The group receiving NF training on the inferior subregion of the left inferior frontal gyrus (lIFG). rIFG; The group receiving NF training on the inferior subregion of the right inferior frontal gyrus (rIFG).

Imaging Results

Neurofeedback setup validation. Three participants from the lIFG group were excluded from the main group fMRI data analysis due to registration issues and excessive movement (>1.5mm). Estimated motion parameters for the remaining 27 participants were; absolute displacement, M=.18mm, SE=.016; relative displacement, M=.08mm, SE=.006.

Based on the ROIs defined online in the NF training task, it was predicted (3a) that the right and left IFG pars opercularis would be activated in the contrast up-regulation vs. rest in the partial brain analysis. As predicted, the rIFG group across genders showed increased activation in a cluster covering the rIFG as well as parts of the right inferior parietal lobe, with the highest measured BOLD signal increase located in the inferior part of rIFG pars opercularis. In addition, the left IFG was also activated, maybe reflecting the use of sub-vocalized speech when up-regulation as the left IFG is the location of Brocas area (figure 10). For the lIFG group, the main cluster of activation was as predicted located in the inferior sub-region of lIFG pars opercularis, but also a cluster located in the left lateral occipital cortex (superior division) and the right central opercular cortex / right precentral gyrus (figure 11). However, given the partial brain FOV of the imaging data centered on the right and left IFG, interpretation of clusters of activity largely outside these areas would be limited at best, and therefore not interpreted further (table 4).

Investigating the prediction (2b) that the NF training associated t-value would be positively correlated to the mean BOLD signal increase in the inferior subregion of rIFG pars opercularis, one offline defined ROI was generated and voxel statistics on the contrast up-regulation vs. rest was performed, and further analyzed in SPSS. ROI was constructed from the Harvard Cortical probability atlas in MNI space (Desikan et al., 2006), using a rigid probability template of P|.25, ensuring that a relatively strict ROI defined by the hypothesis was targeted (figure 12). Pearsons *r* between the NF training associated t-value and the offline defined inferior ROI mean activity was not significant, $r = -.414$, $p = .122$.

Thus, the results validate the NF training setup in regards to prediction 3a, but does not support prediction 2b, raising concerns over the NF training associated t-value's validity as a measure of NF training success (see discussion).

Table 5

Neurofeedback activated regions.

Contrast	Group	Side	Area	# voxels	Max Z-score	Peak Voxel		
						X	Y	Z
Up-regulation > rest	rIFG	R	rIFG Pars Opercularis	2770	6.18	56	16	0
		L	lIFG Pars Opercularis	1489	5.53	-56	12	0
	lIFG	L	lIFG Pars Opercularis	591	7.13	-54	12	0
		L	Left Occipital Cortex Superior Division	468	5.27	-56	-62	30
		R	Right Central Opercular Cortex	376	5.08	60	6	2

Note. Significant activations in the contrast up-regulation minus rest during the Neurofeedback training task, across groups. Peak voxel coordinates in Montreal Neurological Institute (MNI). Highest probability areas are reported from Harvard Cortical Probability Atlas (Desikan et al., 2006). Activations are cluster thresholded at Z > 2.3 and corrected for multiple comparisons at $p < .05$.

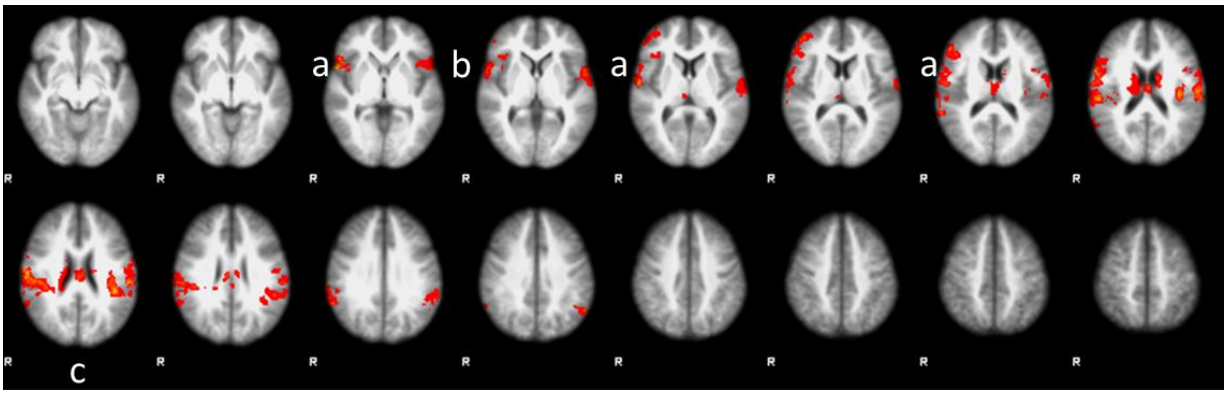

Figure 10. Results from the offline dynamic imaging analysis of the group receiving Neurofeedback training on the right inferior frontal gyrus (IFG). Figure represents cortical areas activated during up-regulation contrasted to rest, in the Neurofeedback Training task. Marked areas of interest are; right IFG (a); left IFG (b). Measured activity was also located bilaterally in the inferior parietal cortex.

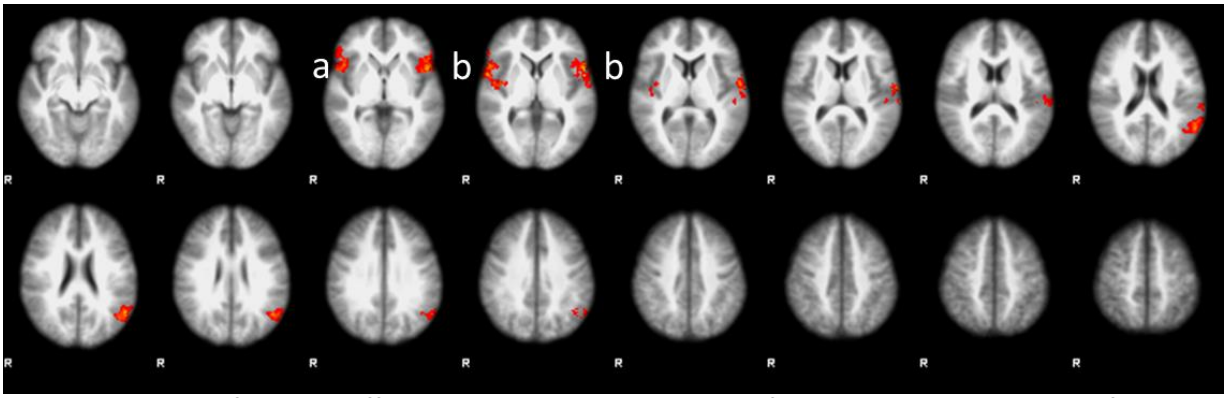

Figure 11. Results from the offline dynamic imaging analysis of the group receiving Neurofeedback training on the left inferior frontal gyrus (IFG). Figure represents cortical areas activated during up-regulation contrasted to rest, in the Neurofeedback Training task. Marked areas of interest are; right IFG (a); left IFG (b). Measured activity was also located in the left inferior parietal cortex and the left superior occipital cortex.

ROI based statistics. To investigate the predictions (3b, 3c) that the BOLD activity in the inferior subregion of rIFG pars opercularis would predict post training performance overall linear regression analysis was performed. However, given the two subregion proposal of Levy et al (2011), a second offline defined ROI was generated over the superior subregion of the rIFG pars opercularis using the same method as above (figure 12). Mean and max values from both offline ROIs (superior, inferior) were entered in the model, and removed with a backwards stepwise method using a removal probability of P|.05. For the SST, the algorithm ended up with two factors; mean BOLD signal increase in the superior ROI, β = 80.93, $t(14) = 4.65$, $p < .001$; and peak BOLD signal increase in the inferior ROI, β = -14.33, $t(14) = -3.1$, $p = .005$. Together they predicted a large portion of the variance in measured SSRT change over sessions, $r^2 = .511$, $F(2, 23) = 10.96$, $p < .001$. Based on the gender differences in post training results on the SST, a regression analysis was performed for the genders separately. The procedure revealed that while males in general showed the same overall pattern as the main analysis, females change in SSRTs over sessions was not significantly predicted by any of the measured factors. For the CORC, no model significantly predicted measured change over sessions; however regression analysis of the genders separately reveals the same pattern as for the SST task prediction model. Males' mean BOLD signal increase in the inferior ROI, $\beta = 34.47$, $t(14) = 2.49$, $p = .025$; explained a significant large portion of variance in CORC; $r^2 = .293$, $F(1, 15) = 6.22$, $p = .025$. While for the females, none of the components predicted the CORC. The rIFG group also showed significant higher levels of mean (M=0.55%, SE=.15) and peak (M=3.16%, SE=.47) activation in the inferior subregion, compared to the lIFG group (Mean; M=0.12%, SE=.12; Peak; M=1.61%, SE=.18). Follow up independent students t-tests confirmed this; mean difference $t(26) = 2.16$, $p = .036$, peak difference, $t(26) = 3.05$, $p = .007$. However, there was no significant difference between groups in the superior subregion, $p > .76$. This suggests that the males in the rIFG group is driving the inferior ROI predictors but not the superior predictor, indicating that the change in post training performance on the SST and the PCT can in part be attributed to activity levels in the inferior subregion of the rIFG, confirming predictions (3b, 3c).

Given the gender difference in the results from the behavioral paradigms (i.e. males in the rIFG group showed significantly decreased SSRTs but significantly increased PCT CORC compared to the lIFG group and females in the rIFG group), it was expected that there would be differences in measured BOLD signal in the inferior subregion of the rIFG pars opercularis

between males and females. For mean and max ROI signal values, females seem to have lower activation levels in the inferior region. However, contrary to expectations follow up independent student t-tests between males and females in the rIFG group showed no significant differences, $p > .382$.

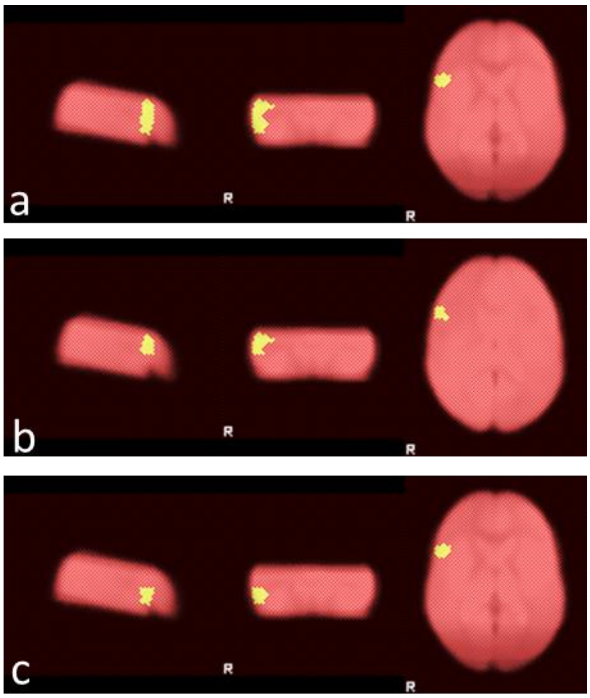

Figure 8. Offline defined regions of interest, as defined by the Harvard Cortical Probability Atlas (Desikan et al., 2006) of right inferior frontal gyrus (rIFG).
a) rIFG pars opercularis
b) superior subregion of rIFG pars opercularis
c) inferior subregion of rIFG pars opercularis

Discussion

The overarching goal of this project was to further investigate rIFGs proposed role in motor response inhibition. In the current study an experiment was conducted to examine the effect of rt-fMRI NF training on the inferior subdivision of rIFG pars opercularis and corresponding effects on performance on a motor response inhibition task and an attentional reorienting task. It was hypothesized that the inferior subdivision of rIFG pars opercularis was mainly involved in either response inhibition or attentional reorienting, and that successful NF training would lead to post training performance improvements on the SST and/or the PCT.

In accordance with earlier rt-fMRI NF studies (Johnston et al., 2010; Rota et al., 2009; Shibata et al., 2011; Weiskopf, 2012), the present study demonstrated that participants successfully managed to up-regulate their measured BOLD-signal during the NF training session.

Regarding the behavioral predictions (1a, 1b), the initial analyses revealed that, overall, the rIFG group did not improve on post training SST performance, and decreased on post training PCT performance, as compared to the lIFG group. Further analyses revealed however, that the males in the rIFG group had decreased SSRTs, and that the males in the rIFG group had increased CORC, as compared to females in the rIFG group and both genders in the lIFG group. Thus, for males the prediction (1a) that NF training should result in improved SST task performance was supported, while the prediction (1b) that NF training should result in improved SST and PCT performance was not supported.

Regarding the NF training t-value predictions (2a, 2b, 2c), linear regression analysis on CORC-change and SSRT-change showed that the NF training associated t-value was only a significant predictor for the measured change in SSRTs in the SST for males in the rIFG group. The estimated beta coefficient of the predictor was however positive, indicating that a larger t-value (higher consistent up-regulation contra rest) predicted a smaller reduction in SSRTs. In addition, the NF training associated t-value did not correlate positively with measured mean activity in the offline defined inferior subdivision of rIFG pars opercularis ROI. Thus results were inconsistent with the prediction (2b, 2c) that the NF training associated t-value did not successfully predict post training task performance in the SST or the PCT. In addition, results were inconsistent with the prediction (2a) that the NF training associated t-value was correlated with measured activity in the inferior sub region of the rIFG pars opercularis. In addition, these results do not support the prediction (4) that females would not influence the variables of interest (SSRT, CORC).

Regarding the functional imaging predictions (3a, 3b, 3c), significant clusters of activity was located at the areas where participants received live hemodynamic information during the NF training task. Mean activity in the offline defined superior rIFG pars opercularis ROI and peak activity in the offline defined inferior ROI successfully predicted a large portion of the measured SSRT change over sessions for males, while mean activity in the inferior ROI predicted a large portion of the measured CORC over sessions for males. In addition, the rIFG group showed significantly higher mean and peak activity in the offline defined inferior subdivision of the rIFG pars opercularis, indicating that the regression models seem to be mainly driven by the males in the rIFG group. Thus, results were in line with the prediction (3a) that during up-regulation the area targeted with NF was highly activated. Results were also in line with the predictions (3b, 3c) that measured activity in the inferior subregion of the rIFG pars opercularis successfully predicted measured post NF training task performance in the SST and the PCT.

While the presented results did not support the initial predictions, two findings are of interest. The males in the rIFG group had an effect of NF training, but not females, and the relationship between the effect of NF training and post training performance was inverse in the two task (i.e. improved response inhibition efficiency but reduced attention reorienting efficiency). Three findings complicate interpretation of the behavioral results; initial pre-training group and gender differences were observed in the SST; the overall post NF training gender differences on the behavioral tasks; the lack of predictive power of the NF training associated t-value as well as the value's lacking relationship with measured BOLD activity in the offline defined inferior subregion of the rIFG pars opercularis. Before interpretation of the present findings, these issues will be handled.

Group differences

The results indicated that there existed initial group and gender differences in SST SSRTs, possibly confounding the results. Gender is approximately equally split and blind group randomization was performed. None of the investigated confounding variables differed between groups, such as handedness, meditation experience, medication, age, time of testing or personally estimated IQ. While there might exist variables not measured and controlled for (i.e. native language, see Hsieh, Gandour, Wong, & Hutchins, 2001), the group differences are more likely due to, given the small sample size, sheer randomness. Sample sizes and random chance cannot be mitigated in the present study, but has to be corrected for in future work.

T-value

The NF training t-value as a measure of NF success predicted observed SSRT change over sessions for the males in the rIFG group; however the beta coefficient was positive, indicating that the degree of NF training success was not reflective of post training task performance. In addition, the t-value was not associated with measured BOLD levels in the offline defined inferior subregion of the rIFG pars opercularis. Taken together, it might indicate that the NF training setup was not implemented successfully. However, the partial brain analyses supported increased activity levels during up-regulation in the targeted areas, and the rIFG group showed significant higher activation levels in the offline defined inferior rIFG ROI compared to the lIFG group. In addition, pilot data support the successful implementation of the paradigm (see appendix; Neurofeedback Pilot). Thus, the problem likely lies with the NF training t-value. One possible explanation is that the t-value is not a good estimate of the NF training performance.

The t-value as a measure of NF training success is based on ROIs manually defined online during the NF training, which might not perfectly cover the area of interest and also might be too large. In addition, the t-value does not necessarily dictate individual effect or benefit from the NF training task, i.e. high consistency but low effect size could lead to high t-values. While some previous studies has used the NF training associated t-value as measure of success (e.g. Koush et al., 2012; Linden et al., 2012), there might be room for improvement.

Multiple regression analysis with the mean and peak values in the offline defined inferior and superior rIFG pars opercularis ROIs showed that for males, mean BOLD signal decrease in the superior ROI with the peak BOLD signal increase in the inferior ROI successfully predicted an increase in response inhibition performance in the SST. For the PCT, the mean signal increase in the inferior ROI successfully predicted an increase in CORC. Given that the rIFG group had significantly higher mean and peak signal increase in the offline defined inferior ROI compared to the lIFG group, and thus driving the inferior ROI predictors, the multiple regression model might explain the difference in the post training results. These findings might warrant future studies to discard values associated with the online analyses as predictors, and instead focus on values computed from offline analyses.

Regarding the offline defined ROI peak value, no rt-fMRI NF studies to the author's knowledge have used it as a post training performance predictor, however a study by Weismann and colleagues (2006) used the peak value to predict RTs in a PCT. One

hypothetical interpretation is that for long lasting effects (at least 2 hours) from focused NF training to occur, the system has to be driven to its maximum. In other words, for relevant neuroplastic effects to manifest, the neural area in question has to be overexcited as compared to a smaller consistent increase. Diffusion Tensor Imaging (DTI), magnetic resonance imaging (MRI) and resting state fMRI was performed for the purpose of exploring neuroplastic changes, however analysis of which is outside the scope of the present project.

Gender differences

There are at least two explanations for the gender difference observed in the behavioral results. Either, females had no apparent effect of NF training on response inhibition and attention reorienting, or there are gender differences in the neural contributions to response inhibition and attention.

While little explicit research has been done on the subject of gender differences in neural correlates of response inhibition, Li et al (2009) compared men and women in a stop signal task fMRI study. Their results showed differential activity in men compared to women, but no indication of differences in the rIFG or adjacent areas. However, in an earlier study by the same authors (Li et al., 2006), they reported slightly higher effect sizes for activations in the rIFG in males compared to females, when contrasting successful vs. unsuccessful inhibitions. In addition, by analyzing the participant gender distribution in a sample of fMRI studies there seems to be an over selection of male participants (approximate 66% males), possibly skewing the results of previous studies (Garavan, Ross, & Stein, 1999; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; C. R. Li, Huang, Constable, & Sinha, 2006; Roth et al., 2007; Sharp et al., 2010). These studies show a trend that should be looked further into.

Regarding gender specific effects of rt-fMRI NF training, no earlier findings to the author's knowledge show any such indication, however Ibric et al (2009) reported gender differences in measured QEEG connectivity during EEG NF. In addition, there have been reported gender differences in cortical neuroplasticity using tDCS (Kuo et al., 2006). Taken together with the finding that males and females in the rIFG group did not differ in their measured BOLD levels, there is a possibility that males and females differ in their response to NF training.

Interpretation

The present findings support the hypothesis that the inferior sub-division of rIFG pars opercularis is involved in attentional reorienting (Corbetta & Shulman, 2002; Hampshire et al., 2010). However, contrary to the postulation of Hampshire et al (2010) there was an

inverse relationship between SST and PCT performance. Improved response inhibition was associated with increased cost of reorienting. Given the inverse relationship, the earlier findings of Aron et al (2004, 2014) cannot be explained by reorienting to the stop stimuli as Hampshire proposed. A different account is suggested.

Simmonds, Pekar and Mostofsky (2008) suggest that the pre-SMA is critical for selection of appropriate action, either in the form of inhibition or other responses, in line with Hampshire et al (2010). They performed a meta-analysis on 14 fMRI studies employing the GNG task, and split the studies in degrees complexity (stimulus response associations), and found rIFG activity only in the more complex conditions (see also Mostofsky & Simmonds, 2008). Given that right inferior frontal cortex (IFC) (including rIFG) has earlier been implicated in the maintenance of object information in working memory (see Courtney, 2004), Simmonds argued that simple response conditions don't necessitate working memory interference. Thus the rIFG might be recruited only when task relevant information in working memory is needed to exercise top down control on the response set. Ridderinkhoff et al (2004) also argue that the lateral prefrontal cortex is involved in implementing adjustments to behavior based on conflicting response tendencies (i.e. stop signal in the SST and target location expectation in the PCT). This hypothesis might explain the diverse range of cognitive functions associated with the rIFG (Duncan & Owen, 2000; Miller & Cohen, 2001), and the finding that the pre-SMA is activated before the rIFG in inhibition tasks (Swann et al., 2012). In addition, the view that the rIFG exercises top-down control on behavior is consistent with the finding that higher baseline rIFG activity predicts higher self-control when faced with cravings (Berkman, Falk, & Lieberman, 2011). Further, it might also explain the increase in CORC.

Studies often find right IFC activity in Posner cueing tasks (e.g. Peelen et al., 2004; Vossel et al., 2006), however the act of reorienting itself is mostly associated with the right middle frontal gyrus (rMFG) (Corbetta et al., 2008; Thiel, Zilles, & Fink, 2004), slightly above the superior subregion of rIFG pars opercularis investigated in this study. Indeed, deactivation of the rMFG is associated with momentary lapses in attention, and thus longer RTs (Weissman et al., 2006). The same study also reported increased rIFG peak activity with slower RTs in concurrent trials, although faster for the next. Vossel and Thiel (2006) performed a fMRI study using a PCT where they manipulated the ratio of valid and invalid trials. They noted that for higher ratios of valid trials there was more rIFG activity compared to lower ratio valid trials. They concluded that the top down information of the predictiveness

of the cues influenced both neural activity and RTs. The more reliable the cues the slower the invalid cue trial RTs, thus resulting in increased CORC, and the more reliable the cues the higher increase in rIFG activity. Thus, the observed increase in CORC for males in the rIFG group might be explained by a higher base activity in rIFG during the task (caused by the NF training), meaning a higher top down control of the cued target location which in effect slows reorienting to relevant, but also wrongly cued targets. This hypothesis is further supported by the positive relationship between mean activity in the offline defined inferior rIFG pars opercularis ROI and post training PCT performance reported in the current study, as well as no differential activity in the validly and neutrally cued targets in the PCT for the rIFG and lIFG group (males) (see appendix Posner Cueing Task re-analysis).

Taken together, the rIFG might be responsible for implementing top-down control of behavioral adjustments based on task relevant information in working memory. This hypothesis is inconsistent with the purely inhibitory view of Aron et al (Aron et al., 2004, 2014), the attention reorienting view of Hampshire et al (2010) and the dual subregions view of Levy and Wagner (2011), although it is consistent with their results. In fact, counting (updating), responding (switching) and inhibition, as measured in the design of Hampshire et al (2010) are all defined in the executive frontal lobe functions taxonomy of Miyake, Friedman and colleagues (2000), thus their results might be explained by a top-down executive control view of behavior by working memory content.

Limitations

Several study limitations warrant caution in interpretation of the presented results. Sample size was on the lower end considering the initial group differences. This might confound several of the statistical analysis performed, especially so the single group regression analysis' (for recommendations, see Green, 1991). A solution to the initial group differences could have been to match the two groups on gender and performance in the SST and the PCT. Considering the small sample sizes, none of the post-hoc pairwise comparisons reported in this study was multiple comparisons corrected. This might result in an increase of type 1 errors in the reported pairwise comparisons. However, due to the small sample size, correcting for multiple comparisons would result in an increase in type 2 errors. Considering the significant regression models based on offline analyzed neural activity in parallel to the behavioral results, it is unlikely that the results presented in the present project are solely due to familywise error.

ROIs manually defined online during NF training based on anatomical landmarks might be a major disadvantage compared to a localizer task or atlas based ROI approach. However the offline validation analysis does support overall correct location of the ROIs defined online. Moreover, the manual ROI was fairly large, and thus might partially encompass areas adjacent to the inferior subregion of the rIFG pars opercularis. Further, the partial brain FOV is insufficient for a whole brain analysis, and thus targeted ROI based analysis outside the commonly overlapping area is noisy at best. Further, the study by Levy and Wagner (2011), suggest that the superior subregion of the rIFG pars opercularis extends up to and covers the inferior frontal junction, indicating that possibly the offline defined ROI based statistics of the superior subregion of the rIFG pars opercularis might be imprecise. Sadly the partial brain FOV of most subjects did not cover this area, and thus reanalysis was not possible in the present project. While there is a cost benefit relationship between spatial coverage and temporal resolution, this could have been mitigated by a transfer run as done in several earlier studies (Johnston et al., 2010; Rota et al., 2009; Shibata et al., 2011; Weiskopf, 2012). A transfer run is an imaging block with conventional temporal resolution (approximately 2 seconds), employing the NF training paradigm without feedback. In these cases participants are instructed to employ the same strategy they found successful in the actual NF runs.

While the above limitations warrant caution in interpretation of the presented results, future research will have to address these issues, as well investigate the indication of gender differences in the effect of NF training.

Conclusion

The present study shows the usefulness of rt-fMRI NF as a viable method for scientific investigations. The results do not support the role of rIFG in response inhibition, nor attentional reorienting. Rt-fMRI NF training on the rIFG resulted in an increased response inhibition *and* decreased attention reorienting efficiency. In keeping with previous studies suggesting a more general role for the rIFG, it is argued that rIFG is mainly responsible for implementation of top-down control and adjustment of behavior, based on information in working memory. The results also indicate a gender difference in the neural correlates of SST and PCT, or conversely a gender difference in the effect of rt-fMRI NF training. As gender differences might affect future studies and generalizations in these research areas, it is of major importance to further clarify this issue.

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Appendix

Information flow

The real time system was accomplished using a range of systems and computers, see main article for system details (see methods; setup; neurofeedback).

Before the NF training task begins, a partial FOV scan with the same parameters as the NF training protocol (see methods; setup; neuroimaging) is acquired. This scan is used for online motion correction and registration. The transfer from the scanner host to the AFNI analysis computer is similar to as for the main NF training runs. A second partial FOV structural T1 weighted MR scan with 1.5x1.5x1.5 mm is acquired for the online drawing of ROIs. It is manually converted to PAR/REC due to technical issues and transferred via a memory stick to the AFNI computer, where it is converted with a custom variant of the 3dPAR2AFNI.py script. ROIs are drawn with AFNI inbuilt drawing tools, and stored as a mask. The mask is then resampled into a 3x3x3 mm resolution.

For the NF training runs, first a Philips developed module, XTC (1.1), grabs raw image information as soon as it is reconstructed in the scanner. In the case of fMRI the raw data is in the form of whole single volumes in the PAR/REC format (3.2). The raw images are dumped via LAN to the AFNI computer, where a custom script converts the files into AFNI format using a customized version of the 3dPAR2AFNI.py script. Then the files are read by a custom script which sends the file and relevant parameters to the real-time module of AFNI. The real-time module of AFNI is based on the afni_proc.py processing stream. The first thing that happens is that images are registered online to the initial partial FOV scan acquired before the NF training using a Heptic+Fourer method. Initial registration is Heptic with final adjustments using Fourier. Second, mean voxel signal in the target ROI and reference ROI (see methods; setup; neurofeedback) is sent to a custom script which calculates the difference to baseline of the moving average (see methods; setup; neurofeedback). The two differences (target and reference) are then compared, and the resulting value is sent via LAN to the Stimulus computer. E-prime reads the value and displays it on the screen in the scanner room in the form of a red pillar, factored with 50 for presentational purposes. The stimulus computer is triggered each dynamic scan time (15 TRs), and does not read the same value twice. Time delay is measured by time logging the incoming trigger pulse compared to when all computations are complete and displayed on the screen in the scanner room. Due to some scripts employing refresh rates, the time lag from acquisition varies between approximately a 100 to 200 ms.

Posner Cueing Task Pilot

Due to employing semantic cues instead of more standardized directional cues (such as arrows), a pilot study was performed. 21 subjects performed on the custom PCT to validate that semantic cueing (opposed to directional direct cueing) and the paradigm in general resulted in the same reaction time (RT) pattern as observed earlier. Average accuracy in all conditions bordered a ceiling of 1.0 with low variability and wasn't included in the subsequent analyses (M=.9, SE=0.01). Mean RTs follow the pattern of earlier studies, with invalid cues resulting in higher RTs than neutral cues, and neutral cues resulting in higher RTs than valid cues. To confirm this, cue type (invalid, neutral, valid) was used as a within subject variable in an ANOVA. Due to a violation of sphericity, the Greenhouse-Geisser test results were reported. A significant main effect of cue type was present, $F(1.4, 28.04)=28.06$, $p < .001$. Follow up comparisons reveal that all cue types resulted in significant RT differences, $p < .003$.

Cue type	Mean RT	SD
Invalid	578,5	97,3
Neutral	546,6	79,1
Valid	506,6	60

Neurofeedback Pilot

Among other tests performed, three are reported here. One; a test of the robustness of the Heptic+Fourier online motion correction algorithm implemented in the rt-fMRI setup, where functional images before and after applied motion correction were analyzed. Two; a recording of primary visual cortex with data analysis resulting from raw images collected from scanner, after conversion to the AFNI file format, after converted to the NIFTI file format from AFNI. Methods, setup and design is identical to the main article unless otherwise noted. Three; a test of the weighted models used in the GLM in FSL analyses.

Among piloting tests performed but not shown; up-regulation of Broca's area using inner speech; visual cortex up-regulation using flashing pictures; up-regulation of the right IFG by thinking of English grammatical formulation and syntax (not consistent); motor area activation by moving fingers, hands and elbows. Due to poorly implemented data collection when these tests were performed, results were thus not analyzed and presented. However, all tests successfully revealed up-regulation as witnessed by the online activation graphs presented on screen on the AFNI computer.

Motion Correction Test. One subject (age 25 female) is reported. The participant was asked to slightly and slowly move and turn her head in different directions when experiment signaled up-regulation (see methods; neurofeedback), otherwise lay as still as possible. Figure 1 show the estimated motion parameters from MCFLIRT on raw scanner data, uncorrected data from AFNI and motion corrected data from AFNI, respectively. As noticeable in the graphs, the online motion correction algorithm used, removes most of the movements except the most pronounced spikes. Motion correction estimates of mean displacements were; absolute=0.86mm, relative=0.25mm (raw scanner data), absolute=0.6mm, relative=0.25mm (uncorrected AFNI data); absolute=0.16mm, relative=0.07mm (corrected AFNI data). Further, a random sample of 6 functional sessions from different participants in the original study was analyzed with MCFLIRT. Applying motion correction show a mean decrease in estimated motion parameters for both absolute displacement (M=0.225mm to M=0.075mm) and relative displacement (M=0.093mm to M=0.061mm).

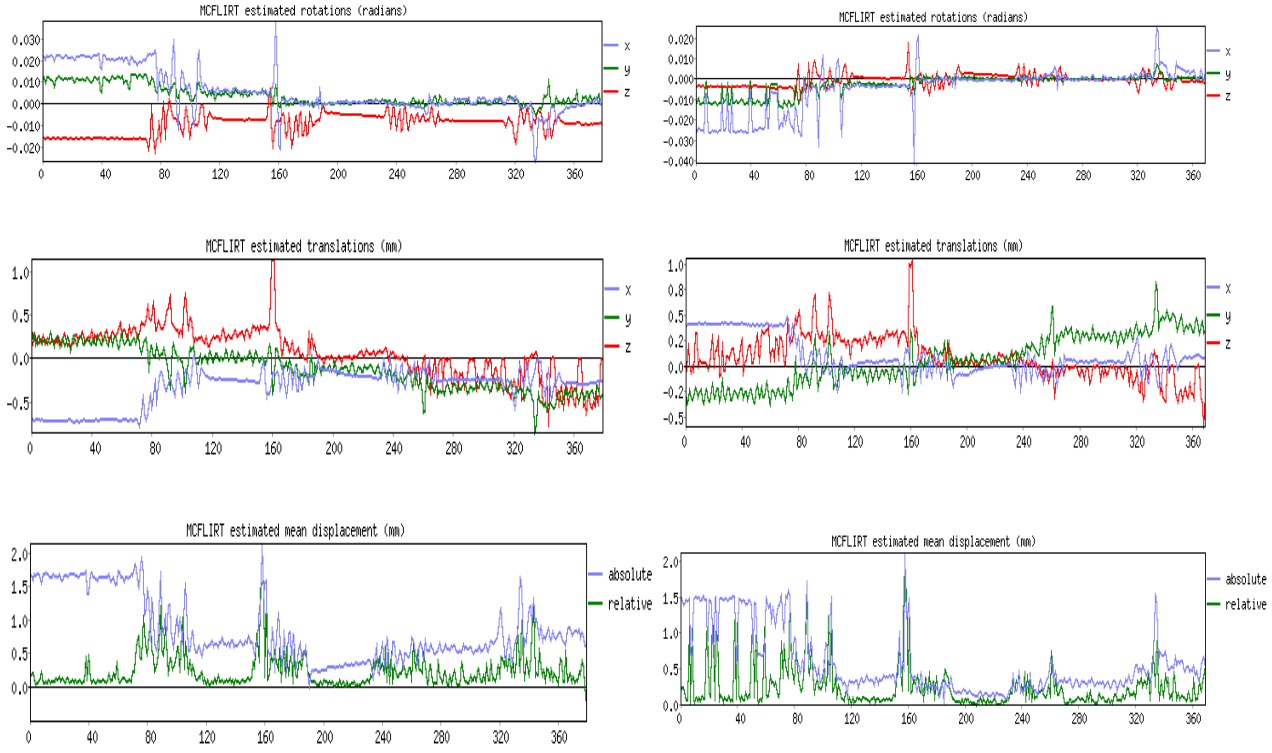
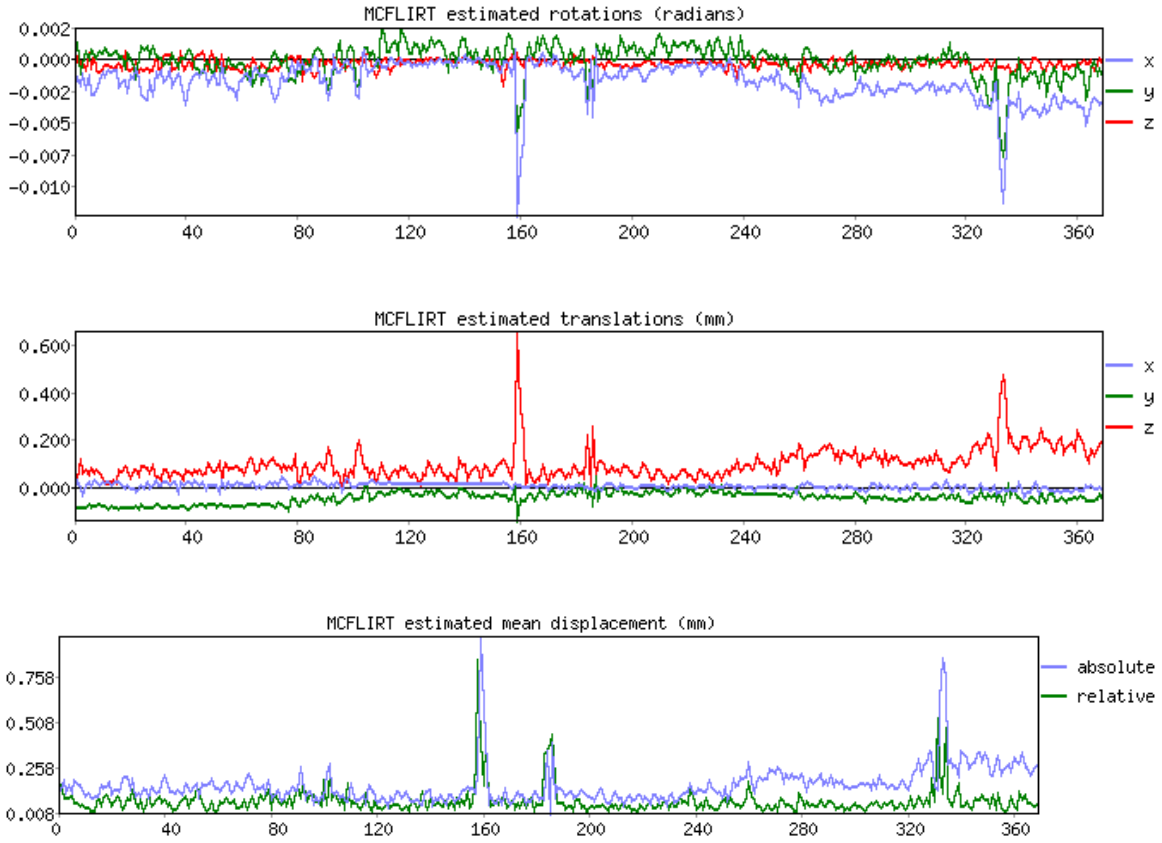


Figure 1. The three panels on the left show estimated motion parameters for raw data (N=1) as acquired in scanner and exported by normal means to NIFTI format. The three panels on the right show estimated motion parameters for raw data as acquired in scanner in PAR/REC, converted to AFNI, then converted to NIFTI. The three panels below show estimated motion parameters for the same files as the three upper right panels, except that they have been motion corrected in AFNI by use of Heptic+Fourier method. All estimated are from the MCFLIRT procedure in FSL.



Visual Cortex test

One subject (age 25 female) is reported. The participant was instructed in the up-regulation condition (see methods; neurofeedback) to move her eyes around and look at different locations while opening and closing her eyes. In the rest condition she was asked to stare passively at one of the uniform grey areas of the computer screen. Up-regulation (eye movement) was contrasted against rest (passive staring). Two runs were done and image statistics were analyzed from an Intracalcarine Cortex ROI generated by the Harvard Cortical Probability Atlas. Run one show a mean signal increase of 3.15% with a range of 0.79% (10%) to 5.71% (90%) of 998 measured non-zero voxels, with max intensity voxel reported at 28% Lingual gyrus, 27% Occipital Pole and 27% Intracalcarine Cortex (figure 2). Run two show a mean signal increase of 2.74% with a range of 0.86% (10%) to 4.67% (90%) of 1003 measured non-zero voxels, with max intensity voxel reported at 28% Lingual gyrus, 27% Occipital Pole and 27% Intracalcarine Cortex (figure 3). Figure 4 show the time series

Figure 4 Time series of differential activation in the target ROI (defined online) and the reference ROI (defined online). Blue line is data. Red line is model.

of the two runs with data gathered online from the NF training setup (see methods). Pearsons correlation for the time series reported by FSL and the time series reported by the NF setup is R=.81.

While the values from the NF setup are contrasted on average from an online defined landmark based ROI, the FSL time series is only in the max voxel of the cluster. Correlation of the contrast (up minus rest) of all voxels in the Intracalcarine Cortex ROI and the NF time series is R=.685, reflecting a not fully successful ROI placement. However, results from the FSL analysis and the shown NF time series both reflect large percent signal change, reflecting that the NF setup indeed reflect the hemodynamic response.

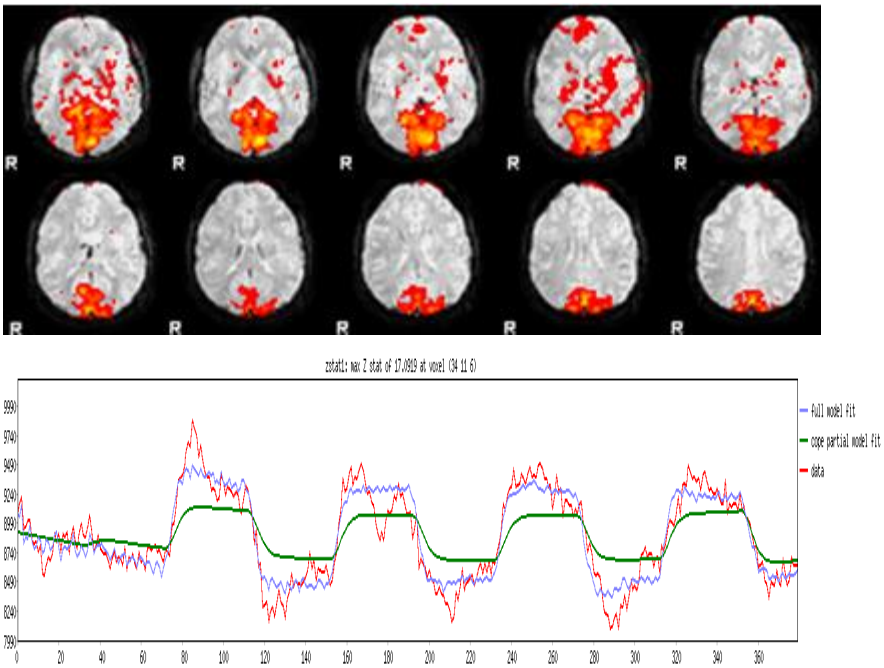


Figure 2 Partial brain analysis of run 1, showing a large cluster of activity in the visual cortex. Upper panel is activity maps thresholded at Z>2.3 P=.05. Lower panel is time series activation in the clusters peak voxel. Brown line is model. Red line is data. Blue line is model fit.

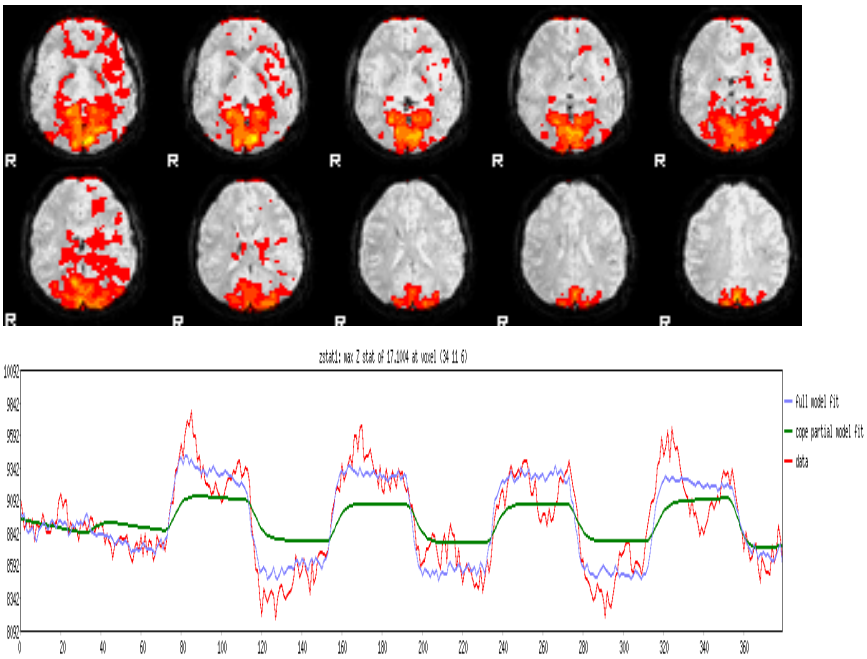
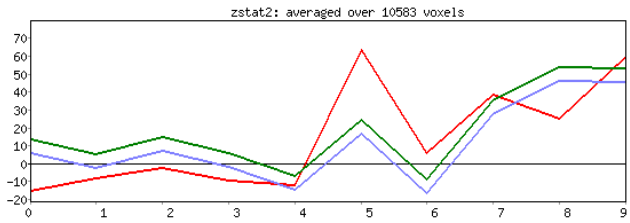
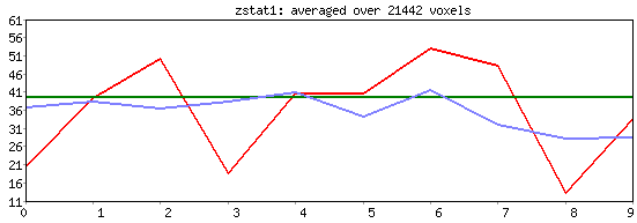


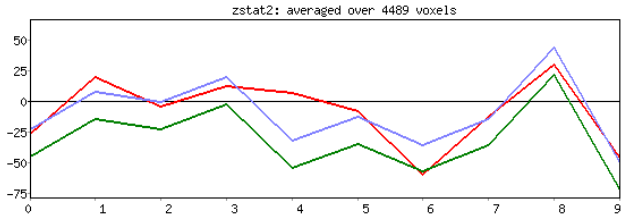
Figure 3 Partial brain analysis of run 1, showing a large cluster of activity in the visual cortex. Upper panel is activity maps thresholded at Z>2.3 P=.05. Lower panel is time series activation in the clusters peak voxel. Brown line is model. Red line is data. Blue line is model fit.

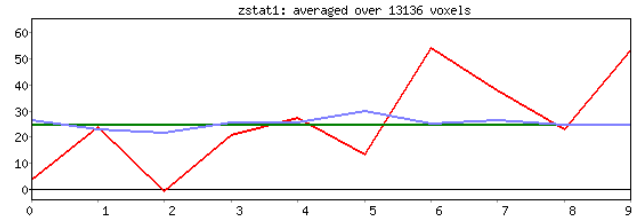
Weighting test

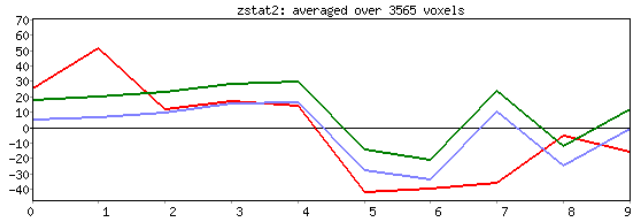
Here is reported fit of weighted and unweighted models to session data (1-10) in the up-regulation minus rest contrast. The examples shown are picked at random from five different subjects and paired, with weighted models on the left and unweighted models at the right. The data is fitted with the measured difference between up-regulation and rest in one session, as analyzed by the online NF training setup. Brown lines is weighted model for the left side panels, and unweighted model for the right side panels. Red is data, and blue is model fit. As evident; model fit is much closer to the "real" data in the weighted condition, than in the unweighted. While the method is somewhat circular in design, it shows that the data generated by the NF training setup, fits the offline analyzed data well, and mostly reduces cluster size.

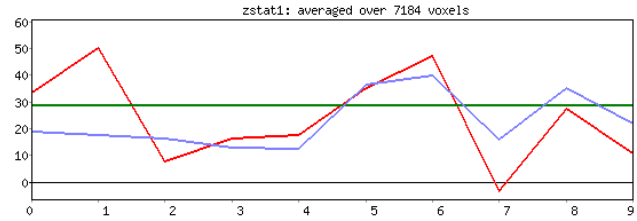

zstat2: averaged over 10583 voxels

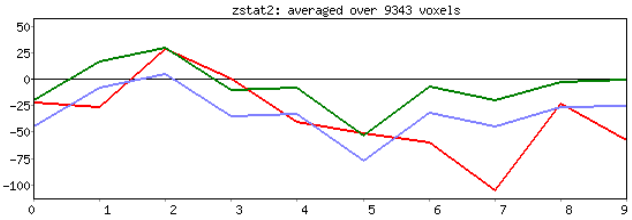

zstat1: averaged over 21442 voxels

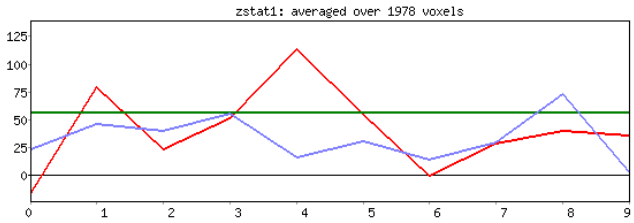

zstat2: averaged over 4489 voxels


zstat1: averaged over 13136 voxels


zstat2: averaged over 3565 voxels


zstat1: averaged over 7184 voxels


zstat2: averaged over 9343 voxels


zstat1: averaged over 1978 voxels

Questionnaire

All participants are asked to fill in a questionnaire with the following items:

1. Age
2. Sex
3. Dominant hand
4. Do you believe you were part of the experimental group or the control group?
5. Did you find a consistent strategy for upregulation?
    a. What was the strategy?
6. Grade/semester
7. Have you had a course(s) in cognitive neuroscience/neuroscience?
8. Do you have a hypothesis regarding which area of the brain you were upregulating and/or what the cognitive function the brain area might be responsible for?
9. Do you have any meditation experience?
10. Do you have any mental states that might affect your ability to focus or perform on long lasting tasks?
11. Are you currently on any kind of medication or painkillers?
12. Do you have a history of neurological damage or brain trauma?
13. Estimated IQ
    a. How sure are you from 1 (sure) to 5 (guess)

Posner Cueing Task re-analysis

To investigate the hypothesis that rIFG is involved in top down control rather than attention re-orienting, RTs for validly and neutrally cued trials were analyzed by using an ANOVA with group (rIFG, lIFG) and gender (males, females) as between subjects variables, and session (pre, post) as a within subject variable. There were no interaction effects between session, group and gender, $p > .114$. There were only one main effect of session, $F(1,25) = 5.2$, $p = .03$, for the neutral condition, indicating an overall change between pre and post training performance. As in the main analyses, CORC and SSRT showed significant change for the males in the rIFG group, pairwise comparisons were performed between all groups and genders on both validly and neutrally cued RTs. Using non-corrected paired comparisons could lead to an inflation of type 1 errors, but no significant relationships between none of the groups, $p > .072$, thus it is argued that as shown in the main analysis, only the CORC component differed between males in the rIFG group, and all other groups and genders.